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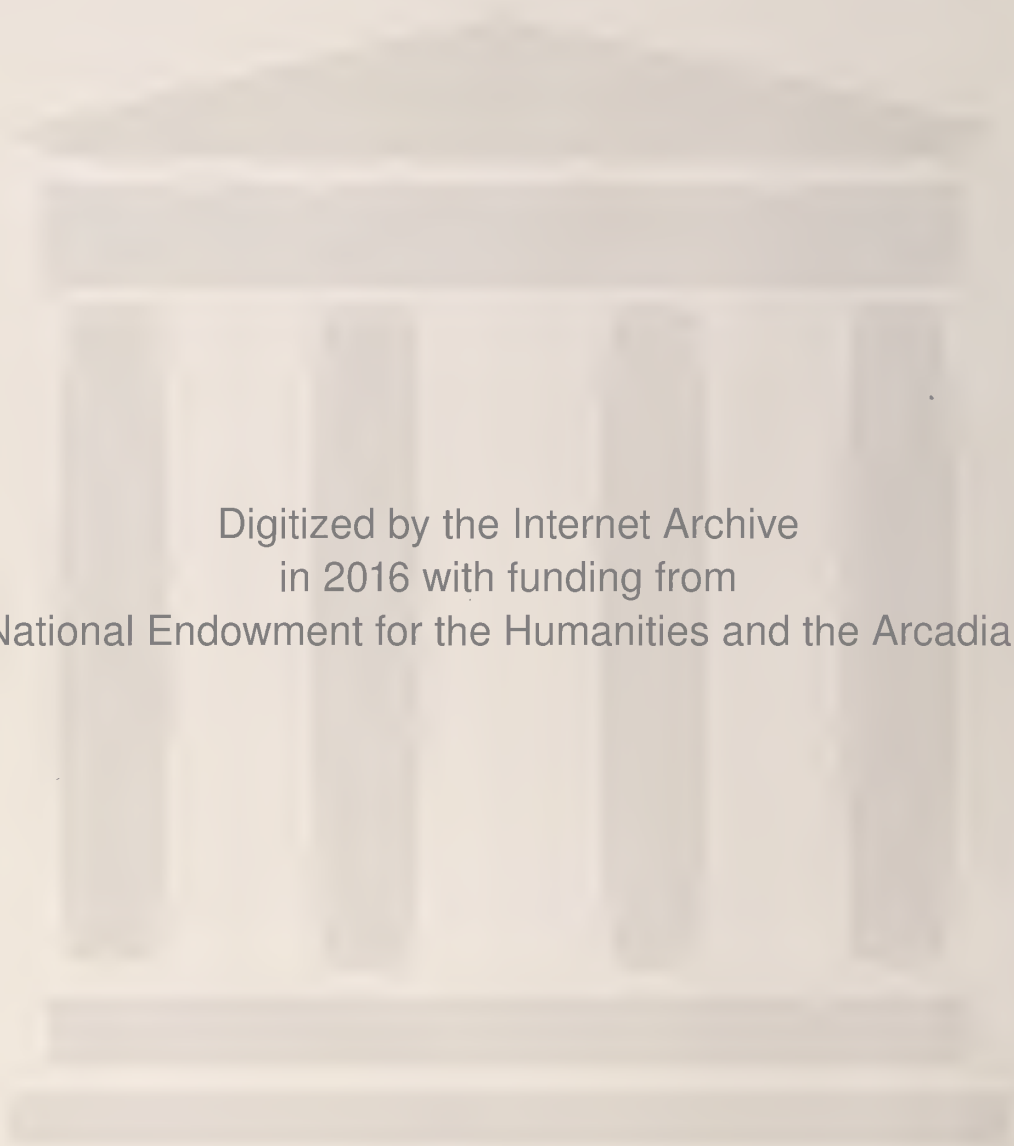


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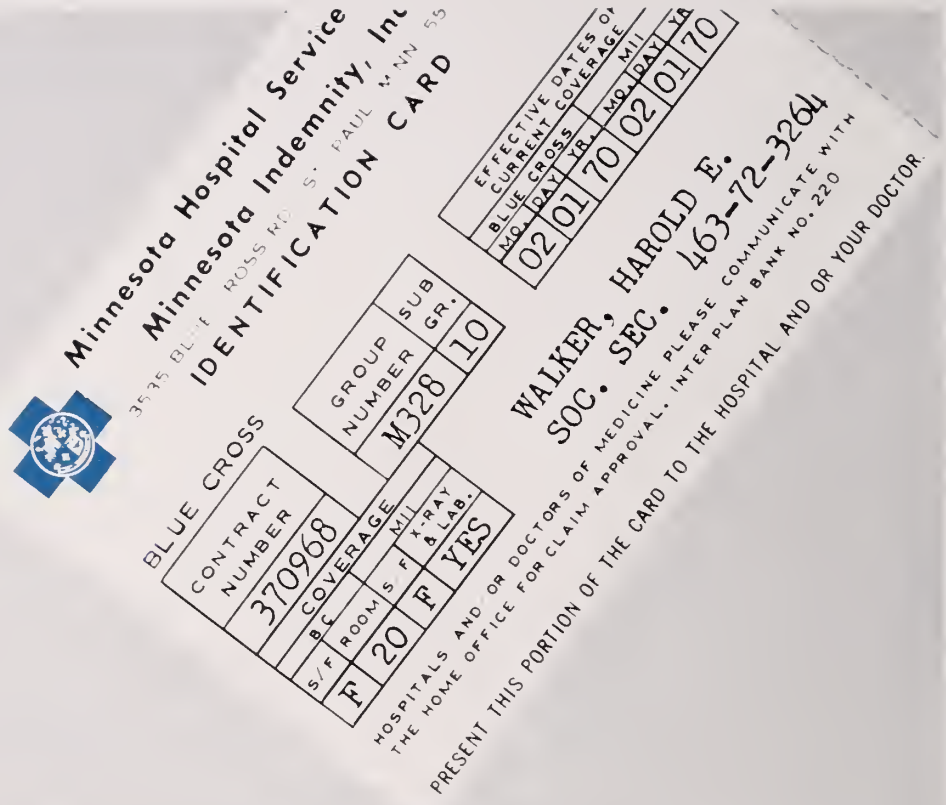


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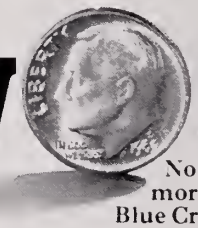
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President's Letter

Medical Malpractice

Former Health, Education, and Welfare Secretary, Robert H. Finch, has publicly made the statement that as a young attorney he made his livelihood in the field of medical malpractice. This is a lucrative field and a common means for the neophyte attorney to become established. Understandably, physicians dislike the adverse publicity associated with being sued for an alleged or a real incident of malpractice. Consequently, in many cases he and his insurance carrier are easy prey for the attorney to collect a sizable fee by a settlement out of court. Most state medical societies have a grievance committee to which patients who believe they have a legitimate complaint may turn, but such committees have been only partially successful in abating what often amount to plain abuses of the legal processes. Psychologically, many juries tend to be more sympathetic toward the "wronged" patient and it is not uncommon to read in the daily press that a claimant has been awarded $100,000 or more. As a result of this, many insurance carriers refuse to handle malpractice insurance or, if they do, the annual premium in certain areas and in certain specialties has risen to as high as $10,000.

Physicians and surgeons try to adjust to such sharp increases in the cost of malpractice insurance by charging higher fees to compensate for higher overhead costs. Some of my physician friends in metropolitan centers refuse to prescribe certain drugs, to give blood transfusions or to perform even minor procedures without having the patient sign a waiver, even though the waiver might not stand up in court. This is a tragic turn of events; it polarizes the gap between patient and physician at exactly the stage at which sympathy and mutual understanding are paramount to successful treatment. It vitiates some measures which the practitioner otherwise might institute with confidence, and it leaves him in a despond of frustration.

Medical malpractice lawsuits usually are contested much more bitterly than ordinary negligence suits. The litigants as well as the public have important interests in the processing and outcome of malpractice suits. Physicians should not be plagued with the defense of unmeritorious lawsuits; likewise, a truly wronged patient certainly is entitled to pursue a justified claim. But, nonetheless, innovations and advances in medicine will be hamstrung unless there is more rapport among patient, lawyer and physician and trust in the good intentions of all. Legal and medical colleges would do well to spend more time teaching conciliatory procedures and moral obligations.

A recent suggestion by the Minnesota Supreme Court of a screening committee composed of physicians and lawyers to review all questionable malpractice claims might be a step in the right direction.

R. J. Jackman

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The Mexico City Olympic Games

Preparation and Performance

MERRITT H. STILES, M.D.*

THE CONCERN which developed over the International Olympic Committee's decision to hold its 1968 Games at Mexico City served to intensify interest in the problems of altitude adaptation. There had been previous studies on human performance at altitude, and a few on the effects of training, but these studies had been made at widely varying altitudes, generally considerably higher than Mexico City's 7,349 feet, and the subjects studied were relatively untrained, with the result that both the effects of altitude adaptation and the effects of conditioning were involved. Human performance at 15,000 feet differs materially from performance at 7,500 feet, and the training response of a superbly conditioned world class athlete is not that of his healthy but untrained counterpart.

It became apparent quite early that there was a marked degree of similarity in the physiologic processes involved in altitude adaptation and those involved in any vigorous conditioning program: so great a similarity as to suggest that both were essentially the same process, differing only in degree.

Utilization of Atmospheric Oxygen

Fundamentally, athletic performance, particularly in endurance events, is dependent on the utilization of atmospheric oxygen by muscle cells in the production of energy. As Knuttgen has pointed out, this process involves a number of steps (Table 1). Yet these steps, involved and complex as they may seem,[2a] are only preliminary to the subsequent phases of oxidative metabolism with usage and storage of oxidative energy in the more comprehensive process of aerobic energy release.

Oxygen Debt

From the standpoint of athletic performance the only important factor at moderate altitude is that the barometric pressure and the partial pressure of oxygen are about 20 percent lower than at sea level. The lower oxygen pressure has no effect on field events, or on running and swimming events not requiring more than one and three-quarters to two minutes of maximum effort.[2b] Oxygen debt, or anaerobic capacity, is the principal factor in short duration events, and performances equalling or improving on previous world records were predictable. Energy for muscular activity comes from the splitting of high energy compounds, adenosine triphosphate and creatine phosphate. Oxygen resynthesizes these compounds; the oxygen deficit required for resynthesis is termed the alactic oxygen debt.[2c]

Lactacid Oxygen Debt

When a work load is maintained over a long period at a high level an added mechanism comes into play: the breakdown of glycogen with the release of energy and the formation of lactic acid, constituting the so-called lactacid

TABLE I.

Delivery of Atmospheric Oxygen to Muscle Cells*

1. Delivery of air to alveoli by pulmonary ventilation.
2. Diffusion of oxygen from alveoli to plasma by diffusion through pulmonary membrane and capillary wall.
3. Diffusion through red cell membrane and union with hemoglobin.
4. Delivery to systemic capillaries by means of blood flow.
5. Diffusion through red cell membrane to plasma.
6. Delivery to tissue cell by diffusion and extracellular fluid flow.
7. Diffusion through muscle cell membrane.

*Knuttgen, H. G., Physical Working Capacity and Physical Performance, Med. and Sci. in Sport, 1:1-8 (Mar.) 1969.

*Chairman, Medical and Training Services Committee, United States Olympic Committee, 1965-1969.
Spokane, Washington.

oxygen debt.[2d,e] Various estimates of the total oxygen debt capacity have been made. The theory of oxygen debt measurement is simple, but its application presents difficulties, and quite widely varying results have been reported. Dill and Saktor's estimate of 5 to 6 litres in well conditioned athletes,[3] approximately equal to the maximum oxygen uptake for a period of a minute, seems reasonable, and would adequately account for the excellent performances at Mexico City in events not requiring more than two minutes of maximum effort.

Effect of Duration of the Event

Prolonged Events—20 Minutes

In prolonged events, performance is dependent largely on inspired oxygen since, when spread out over a 20-minute period, for example, the oxygen debt capacity is hardly appreciable: 10 percent for a distance of 5,000 meters, and 5 percent for 10,000 meters.[4a] Because of the lower partial pressure of oxygen one might expect performance times to be as much as 15 to 20 percent slower in a 20-minute event; actually times have usually been prolonged by only 7 to 10 percent because of the numerous adaptive factors.

Ten Minutes and Less

In middle-distance events, requiring 10 minutes at sea level, the oxygen debt capacity need not be spread so thin, and performance times have been only about 5 percent longer.

In events requiring around four minutes at sea level, performance times are prolonged by 3 to 4 percent These effects are observed in running, swimming, cycling, rowing, and paddling events of over two minutes' duration. Team events that require only interrupted effort, as soccer-football, water polo, basketball[4b] and field hockey, and bout events, where effort is on a stop-and-go basis, should be little affected, since the overall effort may not require more than 75 percent of the available oxygen supply.

Effect of Altitude

While experience has shown that adaptation to altitude does occur, the factors involved are not entirely understood. Increased pulmonary ventilation is important. A decrease in the partial pressure of oxygen in the inspired air leads to an increase in ventilation through its effect on carotid and aortic chemoreceptors,[5,6] but this mechanism apparently does not come into play at moderate altitudes such as that of Mexico City. The rate of pulmonary ventilation does not increase significantly under 8,000 feet elevation,[7] and in experienced subjects at rest there is no effect on respiratory rate up to 10,000 feet.[8] Up to 16,000 feet only very minor increases occur with about 20 percent increase at 20,000 feet. With exercise there is a definite increase in rate at 14,000 feet.

Newly Arrived Lowlanders

It is generally agreed that there is considerable individual variation,[8] and that many if not most lowlanders newly arrived at moderate altitude demonstrate increased ventilation which disappears with continued residence.[9] This hyperventilation cannot be accounted for by known chemical changes in the blood,[2f] and the probable role of neurogenic factors has been suggested.[2f,7,10,11a,12] As it does at sea level, hyperventilation may lead to alkalosis, accounting for symptoms experienced by many newcomers to moderate altitudes, and possibly even leading to transient phasic breathing[11a] or even more serious consequences.[11b]

Cardiac Output

Cardiac output has been considered[2a] the principal limiting factor of oxygen supply in altitude adaptation. Pugh[13a,b] reported that the cardiac output, maximum heart rate, and stroke volume all decreased, but this study was made at approximately 18,000 feet.

Piiper[2a] reported the cardiac output lower in hypoxia in running dogs at both medium and higher speeds. On the other hand, Klausen[14] reported little change in cardiac output, and Asmussen and Consolazio[15] reported increased cardiac output in a study at Mt. Evans. This latter observation is consistent with observations that cardiac output increases with training at altitude.[4c,d]

While the maximum oxygen uptake is decreased at altitude because of the lower partial pressure of oxygen, there is quite general agreement that it improves with training,[2b,4e,f,16,17] with most of the improvement at moderate altitude coming in the first 10 to 14 days.[4e,f,g] It is well known that the hemoglobin level is significantly increased at higher elevations. While not all studies made at moderate altitudes are in

agreement, most have shown early hemoconcentration with a later rise in hemoglobin and erythrocytes.[4c] Other studies have shown that myoglobin levels may be increased,[4g,18] that increased tissue vascularization may develop,[4c,18,19] and that the arteriovenous oxygen difference may be widened.[4d,h]

Increased Oxygen Debt

The factors noted above combine to provide the increased oxygen delivery capacity. Though there is some disagreement,[6] most of the available evidence indicates that increased anaerobic capacity may also be a factor in altitude adaptation.[2j,4c,f,g,18,20] It is of further interest that the changes observed in training at altitude parallel those found in conditioning programs at sea level,[21,22] and that many of these changes may be reversed by enforced rest.[23]

Experience in Pacing

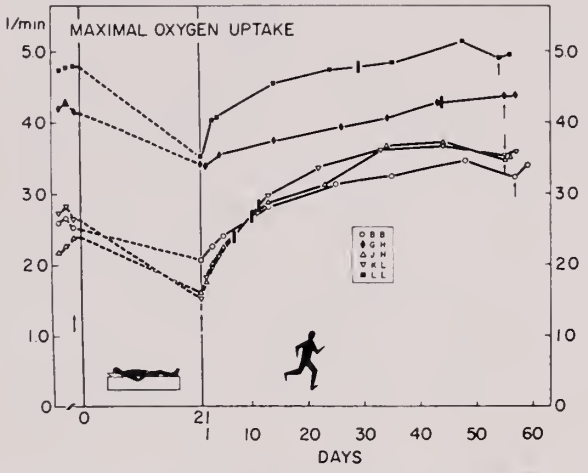
Though reassurance as to the absence of harmful effects may at times be a factor in improved athletic performance, experience in pacing is in all probability a much more important factor. In effect, the two-miler needs to learn to pace himself as though he were running two and one-half to three miles at sea level. Concern has been expressed that the slower pace might result in some degree of muscle detraining, but if so, increased "spurt" training could be corrective.[4c]

Effect of Top Training

Not all athletes adapt equally well to altitude. This may be due to psychological factors in some. In others it may be due to lessened pulmonary diffusion,[2h] though this can be overcome to some extent by increased ventilation. Most adaptive changes apparently occur within a two- to three-week period.[2b,4g] There seems to be general agreement that adaptation is most rapid in the athlete who is in top condition when he arrives at high altitude,[2i,4g] and who runs time trials during his first day or two.[20]

Effect of Bed Rest

The old myth, "Take it easy the first few days at altitude," seems to be well exploded as far as moderate altitudes are concerned. In fact, there is evidence that taking it easy for a few days may result in a significant degree of detraining.[4i] Saltin and co-workers[4a] demonstrated that three weeks of enforced bed rest resulted in about 25 percent deterioration in maximum oxygen uptake in a highly trained athlete, with six weeks of intensive training required before the athlete regained his former condition[23] (Figure 1).



Saltin, B., Bloomquist, G., Mitchell, J. H., Johnson, R. L., Jr., Wildenthal, K., and Chapman, C. B., Response to Exercise after Bed Rest and after Training, Circulation XXXVIII, Supplement No. VII, p. 11 (Nov.) 1968.

Fig. 1—Maximal oxygen uptake after bed rest and retraining.

Adaptation

Recovery times following all-out effort at moderate altitude should be about the same as at sea level[4h]; some experienced coaches even feel altitude recovery time may be shorter.[12,24]

Repay of Oxygen Debt

Recovery from short-duration events consists largely of repaying the oxygen debt. The alactate portion, approximately one-half the total, is half repaid in between 15 and 30 seconds at sea level.[2c,3] Since ventilation is close to capacity during this period, repayment of this portion of the debt might take 20 to 40 seconds at moderate altitude. Repayment of the remaining portion of the alactate debt, which takes several minutes at sea level, and repayment of the lactate debt, a more gradual process, should take no longer at moderate altitude since ventilation is at a much lower level.

Restore Glycogen Depletion

Recovery from prolonged endurance events, where muscle fatigue and glycogen depletion become important factors, will take longer, al-

though the time should not be significantly greater than at sea level.

While there have been a number of intriguing suggestions as to how altitude adaptation might be accelerated by diet[25] or by medication,[11c,26] available time did not permit evaluation and it is hoped that others will make the needed studies. A number of reports have indicated that performance may be improved by alternating periods of high and low altitude training,[20,27] though other reports have not confirmed this observation. Still other studies have indicated that performance at altitude may be improved by altitude training the previous year.[28] The reasons for such improvement are not clear, unless altitude variations stress adaptive mechanisms to a greater degree than does training at a single altitude. The possibility must also be considered that such improvement will occur only in an athlete who has not reached his peak of conditioning. While confirmation of these observations will depend on repeated studies, it seems abundantly clear that no harmful effects are associated with repeated episodes of altitude training, or with interruption of a period of training at moderate altitude by return to a lower altitude. Recommendations made to Olympic coaches and competitors are listed in Table 2.

TABLE 2.
Recommendations on Competition and Training at Moderate Altitude.

1. No danger exists in altitude competition itself.
2. Most symptoms at moderate altitude are psychological, from hyperventilation.
3. New records are possible in field and short-duration events.
4. Performance times will be prolonged in middle- and long-distance events.
5. Acclimatization and improved performance at altitude result from:
   - A. Cross-adaptation with conditioning programs.
     - (1) Improvement in maximum oxygen uptake.
       - a. Increased pulmonary ventilation.
       - b. Increased cardiac output.
       - c. Increase in respiratory pigments.
       - d. Increased tissue vascularization.
       - e. Widened arteriovenous oxygen difference.
     - (2) Increased anaerobic capacity.
   - B. Reassurance.
   - C. Experience in pacing.
6. Altitude acclimatization is fastest:
   - A. In well conditioned athletes.
   - B. With vigorous training.
   - C. With early time trials.
7. Recovery times are essentially the same as at sea level.
8. The maximum allowable training should be conducted at altitude for competitors in events requiring more than two minutes of maximum effort.
9. Shorter periods of altitude training are suitable for other competitors.
10. Repeated periods of altitude training may improve performance.

Studies reported to date indicate that neither the athlete nor the spectator should be subject to risk or discomfort at a moderate altitude such as that of Mexico City, and that physiologic problems will develop only at considerably higher elevations where pulmonary hypertension may enter the picture.[2i,11d,29,30] It is of particular interest that there is more than a suggestion in some of the reported studies that hyperventilation may also be a factor in some of the more serious conditions encountered at higher elevations.

Fortunately, the many fears expressed over altitude, as well as the concern over enteritis and even over Mexico's ability to prepare adequately for the Olympic Games, were not allowed to reverse the International Olympic Committee's award of the 1968 Games to Mexico City. The collapses witnessed or described adequately appeared to be emotional rather than physiological. Interestingly, winners never seemed to collapse.

Comments

While the possibility of new world records in short duration events had been predicted, the veritable deluge of new records in track and field must have been a major surprise to all (Tables 3 and 4).

The 800 Meter Runs

Tying previous world records would have been remarkable enough, since events requiring almost two minutes are at the absolute upper limit as far as equalling sea level time is concerned. The motivating effect of competing against the world's best must have been great indeed.

The results of the swimming events, which present a slightly different picture, are listed in Tables 5 and 6. The relatively small number of new world records in swimming can perhaps be explained by the observation that new records

TABLE 3
Men's Track and Field

Event	Winner	Nation	Result	Percent Over World Record	New Record
100 meters	Jim Hines	US	9.9 sec		World
200 meters	Tommie Smith	US	19.8		World
400 meters	Lee Evans	US	43.8		World
400 meter relay		US	38.2		World
1,600 meter relay		US	2:56.1		World
110 meter hurdles	Wm. Davenport	US	13.3		Olympic
400 meter hurdles	D. P. Hemmery	Gr. Britain	48.1		World
800 meters	Ralph Doubell	Australia	1:44.3		World*
1,500 meters	Kipchoge Keino	Kenya	3:34.9	0.8	
	Jim Ryun	US	3:37.8	2.2	
3,000 meter steeple-chase	Amos Biwott	Kenya	8:51.0	4.0	
5,000 meters	Mohamed Cammoudi	Tunisia	14:05.0	2.0	
10,000 meters	Naftali Temu	Kenya	29:27.4	7.0	
Marathon	Mamo Wolde	Ethiopia	2:20:20.4	8.5	
Long jump	Bob Beamon	US	8.90 meters		World
High jump	Dick Fosbury	US	2.24 meters		Olympic
Pole vault	Bob Seagren	US	5.40 meters		Olympic

N.R. New world records are also new Olympic records.
The new records listed as "Olympic" are only Olympic and not world records.
*Tied existing world record; new Olympic record.

TABLE 4
Women's Track and Field

Event	Winner	Nation	Result	Percent Over World Record	New Record
100 meters	Wyomia Tuyus	US	11.0 sec.		World
200 meters	Irina Kirzenstein	Poland	22.5		World
80 meter hurdles	Maureen Caird	Australia	10.3		World*
400 meters	Colette Besson	France	52.0		†
800 meters	Madelaine Manning	US	2:00.8		World
400 meter relay		US	42.8		World

*New Olympic record; tied existing world record.
†Tied existing Olympic record.

TABLE 5
Men's Swimming

Event	Winner	Nation	Result	Percent Over World Record	New Record
100 meter FS	Mike Wenden	Australia	52.2 sec		World
200 meter FS	Mike Wenden	Australia	1:55.2	0.8	Olympic
400 meter FS	1. Mike Burton	US	4:09.0	1.0	Olympic
	2. Ralph Hutton	Canada	4:11.7	2.1	
1,500 meter FS	Mike Burton	US	16:38.9	3.0	Olympic
100 meter But.	Doug Russell	US	55.9	0.5	Olympic*
200 meter But.	Carl Robie	US	2:08.7	2.3	
100 meter Br.	Don McKenzie	US	1:07.7	2.2	Olympic
200 meter Br.	Felipe Munoz	Mexico	2:28.7	0.9	
100 meter Ba.	Roland Matthes	E. Germany	58.7	1.2	Olympic
200 meter Ba.	Roland Matthes	E. Germany	2:09.6	1.6	Olympic
200 meter Med.	Charley Hickox	US	2:12.0	1.1	Olympic
400 meter Med.	Charley Hickox	US	4:48.4	3.4	
400 meter Med. relay		US	3:54.9		World
400 meter FS relay		US	3:31.7		World
800 meter FS relay		US	7:52.3	0.1	

Legend: FS—free style; But. butterfly; Br.—breast stroke; Med.—medley; Ba—back stroke.
*Tied previous Olympic record.

TABLE 6
Women's Swimming

Event	Winner	Nation	Result	Percent Over World Record	New Record
100 meter FS	Jan Henne	US	1:00.0 sec	1.8	
200 meter FS	Debbie Meyers	US	2:10.5	3.0	Olympic
400 meter FS	Debbie Meyers	US	4:31.1	2.8	Olympic
800 meter FS	Debbie Meyers	US	9:24.0	2.3	Olympic
100 meter But.	Lyn McClements	Australia	1:05.5	1.5	
200 meter But.	Ada Kok	Holland	2:24.7	2.6	Olympic
100 meter Ba.	Kaye Hall	US	1:06.2		World
200 meter Ba.	Lillian Watson	US	2:24.8	0.7	Olympic
100 meter Br.	Djerdjica Bjedov	Yugoslavia	1:15.8	2.1	Olympic
200 meter Br.	Sharon Wichman	US	2:44.4	3.7	
200 meter Med.	Claudia Kolb	US	2:24.7	0.8	Olympic
400 meter Med.	Claudia Kolb	US	5:08.5	1.0	Olympic
400 meter Med. relay		US	4:28.3	0.08	Olympic
400 meter FS relay		US	4:02.5	0.6	Olympic

are being established almost month by month in swimming, with impressive gains from one Olympiad to the next, a situation which does not seem to exist in track and field. This also may explain why Olympic, though not world, records were broken in some of the longer swimming events.

In the longer events also, times were somewhat better than anticipated, presumably again a credit to the quality of competition, the intensity and duration of training, and the degree of motivation, rather than an indictment of our understanding of the physiologic factors involved.

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9-33 May be secured from the author.

Nearly all the people coming to a certain sanitarium for treatment were under the impression that they were completely run down. They soon learned differently. At the first weekly lecture, the doctor bluntly told them that they were all wound up, and could do little until they realized this condition and relaxed. If we periodically allow ourselves to become "run down," then Nature is given the necessary leeway to work properly in readjusting and balancing the system.*

*York Trade Compositor.

"I came here, Doctor, to find out just what's wrong with me," she said.

He looked steadily at her. "Three things. You're too fat. You use too much makeup. And something's wrong with your eyesight. My sign here should tell you I'm a veterinarian."*

*Dr. Francis Leo Golden: Jest What the Doctor Ordered.

The Moral Importance of Health

Health is in itself a great contribution to the intrinsic worth of life. To awake in the morning with red blood stirring in the veins, to come to the table with hearty appetite, to go about the day's work with the springing step of abounding energy, and to reach the close of day with that healthy fatigue that quiets restless desire and betokens the blessed boon of sound and dreamless sleep—this is to be a long way on the road to contentment. Heightened vitality means an increased sense of power, a keener zest in everything; troubles slide off the healthy man that would stick to the less vigorous. Bodily depression almost always involves mental depression; our "blues" usually have an organic basis. It was not a superstition that evolved our word "melancholy" from the Greek "black (i.e., disorders) liver;" nor is it a mere pun or paradox to say that whether or not life is worth living depends on the liver.

Health means efficiency, more work done, greater usefulness to society. Sooner or later every man who is worth his salt finds some task the doing of which arouses his ambition and becomes his particular contribution to the world. How bitterly will he then regret the heritage denied him or foolishly squandered, the handicap of quivering nerves, muscular flabbiness, wandering mind, that impedes its accomplishment! Determination and persistence may, indeed, use a frail physique for splendid service; such names as Darwin, Spencer, Prescott, remind us of the strength of human will that can override physical obstacles and by long effort produce a great achievement. But for one victor in this struggle of will against body there are a hundred vanquished; and even these men of genius and grit could have accomplished far more if they had had normally serviceable bodies.

Health makes morality easier and likelier. The pernicious influence of bodily frailty and abnormality upon mind and morals has always been recognized. The lack of proper nutrition or circulation, the state of depressed vitality resulting from want of fresh air, exercise, or sleep, are important factors in the production of insanity and crime. Chronic irritability, moroseness, pathological impulses of all sorts, generally betoken eye-strain, dyspepsia, constipation, or some other bodily derangement. With the regaining of normal health the unruly impulses usually become quieter, sympathy flows more freely, the man becomes kinder, more tolerant, and morally sane.

If health is, then, so important to the individual and society, its pursuit is not a selfish or trivial matter; it is rather a serious and unavoidable duty. . . . But in the great majority of cases a wise conduct of life would retain robust strength for the threescore or more years of our allotted course, increase it for those who start poorly equipped, and regain it for those who by mischance, blunder, or imprudence have lost their heritage. Yet half the world hardly knows what real health is. Our hospitals and sanitariums are crowded, our streets are full of half-sick people—hollow chests, sallow faces, dark-rimmed eyes, nervous, run-down, worn-out, brain-fagged, dragging on their existence, or dying before their time, robbed by stupidity and ignorance of their birthright of full-breathed rosy-cheeked health, and robbing the society that has reared them of the full quota of their service. Health is not merely freedom from disease; we have a right to what Emerson called "plus health."

Most of us would find our powers adequate to our duties if we learned to rest when we are not working, and spend no energy in worry and fretfulness. We need to follow St. Paul's exhortation to "Study to be quiet;" to learn what Carlyle called "the great art of sitting still."*

*Durant Drake: Problems of Conduct, 1935.

The Epidemiology of Ski Injuries

JAMES G. GARRICK, M.D.*

THE RELATIONSHIP between a lack of skiing expertise and inordinately high injury rates is well established.[1] The association between formal ski instruction and a reduction in injury potential is not so clear.

As early as 1941 Brothers[2] noted: "Over half of those injured had not received regular instructions. . ." Smith, in 1955[3] stated: "Seventy-five percent of the ski injury victims have had no lessons whatsoever and "These (injuries resulting from skiing at a speed beyond one's ability or skiing on terrain beyond one's ability) are definitely preventable through instruction in the ski school."

Neither Brothers nor Smith, however, states the frequency with which uninjured skiers avail themselves of ski lessons. In their publication, "Sitzmarks or Safety,"[4] the National Ski Patrol System presents some material[4] dealing with the "control population." In 1958 the study of a sample of 1513 uninjured skiers revealed 46.6% had taken no lessons; however, during the same year it was noted that 47.2% of the 2219 injured skiers had *likewise* taken no lessons. The difference between these two groups is tenuous at best. Equally tenuous is the apparent decrease in the likelihood of injury seen in the group having taken more than six lessons. It is logical to assume that this latter group (i.e. those having taken more than six lessons) have attained a higher degree of expertise and thus enjoy the attendant decreased injury rate.

The decrease in the likelihood of being injured may be the result of the skier's participation in ski lessons. Also possible, however, is the fact that the number of lessons may be only an indirect measurement of skiing experience. Indeed, those seven or more lessons may have required five years to complete, and five years of skiing experience is associated with a decreased likelihood of injury.[4]

Vail, Colorado Study

The author's study conducted at Vail, Colorado, during the winter of 1964-65 yielded results compatible with those of the National Ski Patrol System. Of the control population (803 skiers) 77.7% had taken formal lessons, and 79.5% of 567 injured skiers had also availed themselves of prior formal instruction. Although the difference between the two groups is small, one cannot, from this information, state that participation in ski lessons does not influence likelihood of injury.

During the 1966-67 ski season 2124 injured and 3000 uninjured skiers were interviewed in eleven ski areas across the United States. These interviews represent 883,513 ski man days. The members of both groups were asked whether or not they had taken lessons every year they had skied,† and if so, how many lessons each year.

The injured group contained 1122 skiers (52.82%) who had not taken at least one lesson during each year of skiing experience. The control group contained 1497 (49.9%) similarly untutored skiers. These skiers represent the entire ski population regardless of age, sex, ability, experience, etc.

An examination of the Table reveals that the likelihood of participation in a continuum of ski lessons appears to vary with the length of skiing experience. Of those individuals skiing for their first year, 56% had not taken any lessons.‡ By the third year of experience only 39% had not taken lessons each year. Subsequent levels of experience (i.e., five and 10 years) seem associated with a reversal of this trend.

Expertise achievement, especially during the first few years of skiing experience, appears to be even more closely related to ski instruction.

*Director, National Ski Safety Research, Head, Division of Sports Medicine, Department of Orthopedic Surgery, Medical School, University of Washington, Seattle, Washington.

Preparation and analysis of this material would have been impossible without the assistance and advice of Mr. Ralph Requa. The author gratefully acknowledges this help.

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†Previous studies[5] had revealed the difficulties in analyzing the total number of lessons taken over a variable period of time. Thus, the question evolved in the above form.

‡For an individual skiing his first year any number of lessons would contsitute a "continuum of lessons."

Influence of Lessons and Experience

Fifty-six percent of the first year skiers had not taken lessons prior to being interviewed. Over three-quarters (77%) of this untutored group were classified as novices (AB class*). Only 11% (untutored) had achieved the ability to execute stem christies or better (D, E, or F class) during the first year.

Those who had taken lessons appear to have progressed more rapidly in ability. Less than half of this group (48%) remained in the novice class while 35% attained at least "stem christie" ability.

By the fifth year of skiing experience there appears to be little or no difference in attaining various degrees of expertise related to a continuum of lessons. Thus, the proportion of skiers in each ability class is the same for tutored and untutored groups. The same condition exists at the tenth year of experience.

It must also be noted that by the fifth year over 90% of the skiers have advanced beyond the novice class and by so doing have decreased their injury rates by 72% (from 5.89 to 1.64 injured per 100 ski man days).

Comments

During the 1966-67 study the question relating to participation in lessons was phrased in such a way that skiers could not change from the "no lessons" to the "lessons" group.† Thus, the percentage of skiers in the "no lessons" group can increase only as a result of an absolute decrease in the size of the "lessons" group. The proportion of skiers in the "no lessons" group can decrease only as a result of skiers dropping out of the sport entirely because increases of the size of the "lessons" group resulting from a shift in skiers from the "no lessons" group are impossible.

*Professional Ski Instructors of America ability classification.

†A single year of no lessons, regardless of years of skiing experience, interrupts the continuum of lessons placing the skier in the "no lessons" group.

TABLE

Experience, Ability and Participation in a Continuum of Ski Lessons

Abilities	Years of Skiing Experience				
	1st Year	2nd Year	3rd Year	5th Year	10th Year
Novice					
No lessons	135	59	22	5	2
Lessons	65	46	33	4	1
Intermediate—Beginning					
No lessons	23	53	37	17	5
Lessons	23	67	53	20	2
Intermediate—Advanced					
No lessons	15	57	63	35	18
Lessons	35	80	94	47	14
Experienced					
No lessons	3	20	30	50	45
Lessons	13	41	56	73	39
Totals					
No lessons	176	189	152	107	70
Lessons	136	234	236	144	56
All	312	423	388	251	126

It would then appear that the majority of dropouts are among the untutored and, for the one-year experience group, also novices, since 77% of the "no lessons" group are novices.

Between three and five years of experience the "no lessons" group appears to increase, probably as a result of previously tutored skiers ceasing to take lessons because they are more content with their abilities. Indeed, at five years 84% of tutored skiers have advanced *beyond* the stem turn stage.

Summary and Conclusions

Analysis of a study of injured and uninjured skiers indicates that skiers taking lessons their first year or two of skiing increase their abilities more rapidly than do untutored skiers with comparable experience. An increase in expertise, particularly from the novice (AB) to intermediate (C-D) class, is associated with a decrease in injury rates.

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Positive anything is better than negative nothing.—Elbert Hubbard

Injury Prevention

RICHARD L. VOORHEES, M.D.*

The accident rate in skiing has decreased significantly over the past 10 years. In the beginning phases Classes A and B of the International Class System: Straight running—straight snow plow, snow plow turn and traverse, in all studies represent the highest accident rate. The rate drops from some 15 to 20 accidents per 1,000 skier days to a rough average of three per one thousand skier days at the stem turn level and stays virtually constant from there into the advanced phases. Perhaps the most critical point in the examination of ski instructors for certification is the instructors' ability to demonstrate, analyze, and teach the stem turn.

Basically the stem turn teaches the skier how to set the angle of the traverse: the chief factor in controlling speed. The skier who can maintain a flatter traverse has relatively better control than the one who does not completely turn, acquires a steeper traverse and loses control. On the basis of these facts it is tempting to say that the decrease in accident rates is due to better ski instruction creating a more skilled and hence a safer skier. However, as Dr. James Garrick has pointed out, ski accident rate statistics are involved with so many variables that one cannot draw such a conclusion. Also, it is this same statistical variance which prevents the advocates of safety bindings from being able to maintain that the bindings alone have decreased the accident rate.

However, in spite of this, it is possible to state that in one large Northwest ski school, that has been in existence over 20 years, and where all accidents are reported, the accident and injury rate is significantly less than for the "do-it-yourself recreational skier." Its main program is for ages seven to 14 and involves all-day ski instruction. Eight hundred students, during the 1969 season, skiing nine weeks and constituting 7,200 skier days have suffered five fractures, one of these occurring out of class. This is a rate for serious injuries of less than one per 1,000 skier days. An adult group of 200 housewives skiing for eight weeks suffered no fractures. This same program has been offered to housewives over a period of eight years without fractures.

*Seattle, Washington.

Causes of Accidents

Lack of Ski Sense

Standard causes for ski accidents have been considered ignorance of snow conditions, skiing out of control for the terrain and, with the ever increasing skiing population, collisions. Ignorance of terrain and snow, misjudgment of speed, misconduct of the skier, faulty method of carrying the skis, wrong use of poles and lifts may all be considered a lack of ski sense. It is quite obvious that a programmed method of guiding the neophyte down the slope at a specific speed is going to make his beginning ski life much easier for him and presumably much safer.

Basic Technique

Racing has been the prime consideration in effecting a healthy change in ski technique. Yet photographs which can depict the racer responding to stresses far beyond the physical capability of the recreational skier do not constitute a ski technique. The serious ski teacher must follow a systematic approach of proven methods that will in the long run safely teach the skier to handle a variety of terrain and snow conditions. The teacher's market is not the racer or even the advanced skier but rather an ever-expanding clientele of children and, perhaps, not too athletically inclined adults.

The goal is a sound basic technique which includes all turns through parallel. Advanced techniques which may serve as a bridge to racing, skiing or ice or in powder, will be taught to relatively few. Serious racing is limited to the young and well-conditioned individual.

Foot-in-Bathtub Turn

An historical review of early ski techniques indicates that body position was often extremely unnatural, with weight on the inside ski and marked flexion of the inside knee and hip joint. Movement of the upper body was used to produce turning power; lower body turning power was virtually impossible because of crude equipment (Figure 1).



Figure 1

The Inside Edge

Skis were often long and clumsy. The early California miners sometimes used skis 10 to 12 feet in length. Skis were often designed both for cross-country and for straight running purposes and not for high speed or short radius turns. The single pole technique of Mathias Zdarsky at the turn of the century was based on a natural tendency to lean into the hill and use the single pole in the snow as support or as a brake in turning. Many years were required to achieve the art of leaning out with the upper body to put more weight on the inside edge of the lower ski, thus improving the ability to "hang on to the mountain."

Bindings

The Huitfeldt binding, invented in 1904 and popular for over 25 years, held the boot to the ski but did not hold the heel down; hence it was difficult to shift the center of gravity forward with this type of loose anchor. The Oslo technique of the 1920s involved the use of this binding wherein one could note the distorted body position necessary to create turning power. Also, the open christie with most of the weight on the inside ski was popular at that time.

Arlberg Technique

A safer approach to skiing was achieved by the renowned Hannes Schneider who developed the Arlberg technique starting about 1907 (Figure 2).

Rotation

He emphasized centering the body position



Figure 2

over the skis, with marked knee and ankle flexion, thus placing the skier in a deep crouch. The subsequent low center of gravity added to stability; rotation about the vertical axis of the body and steering in the direction of the turn provided the chief turning power.

Stem Christie

The stem christie became the workhorse of the not quite parallel skier, using a stem of the lower ski (*Abstemm*). This provided a platform base for stability. Parallel christie was possible with the Arlberg technique. Up unweighting was used to release the ski edge with a rather marked down-up-down body motion.

French Technique

The emphasis on parallel skiing was accentuated by Antone Seelos, an Austrian who won many races in the 1934-36 era, skiing parallel as opposed to the stem method of most of the other skiers. He became the coach of the French team, and a new era was launched by his pupil Emile Allais in about 1937.

Forward Lean

Emile Allais used a square body position with little angulation, rather marked flexion of the hip, knee, and ankle joints, and torso in traverse. Parallel turns were made by down unweighting with marked forward lean, and a lifting of the heels for release of the edge was used in some turns (Figure 3).



Figure 3

Centripetal Force

A rotation of the outer shoulder, hip, and arm in the direction of the turn, with blockage of the abdominal muscles to transmit this turning force into the skis, was the chief source of turning power.

Austrian Technique

Just before the War in 1939, as the Swiss were demonstrating a different approach to skiing with counter rotation of the upper body, and maintenance of the outside hip back, the stage was set for post-war skiing. After World War II the ski population exploded. As the terrain changed remarkably because of the creation of moguls, it became necessary to produce turning power in the lower body in order to safely navigate the moguls. Long radius turns became relatively uncontrollable on bumpy terrain, and the abrupt sharp transitions made rotation of the outer part of the body hazardous.

The Austrians, under the guidance of Professor Kruckenhauser analyzing thousands of feet of film footage, developed the counter rotation technique. The Austrians won many races and the technique was soon copied by all other Alpine nations, as well as by the Japanese. In the Seventh and Eighth Interskis at Badgastein, Austria, and Aspen, Colorado, the French demonstrated transitional forms of racing and have virtually originated many of our advanced techniques. However, their basic stance has become more moderate.

American Technique

Professional Ski Instructors of America was founded in 1958 and published its first official American Ski Technique in January 1964. The extremes of the Austrian techniques, such as extreme angulation, extreme counter position, and extreme counter rotation, were modulated to less rigorous positions and motions. All Alpine nations are now considering a common basic technique. The basic principles of the American ski technique could apply to any other national technique and are intimately concerned with ski safety.

Ski instruction may be subdivided into technique, methods, and theory. This unique approach, which is essential to the understanding of ski instruction, was first popularized by the Professional Ski Instructors of America (Figure 4).

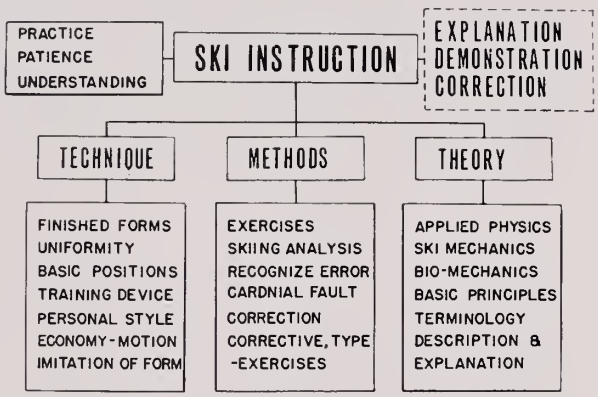


Figure 4

Basic Principles of Ski Technique

Natural Positioning

This refers to human anatomy related to balance on an inclined plane. The emphasis is placed on a highly relaxed stance, with the skeleton carrying the weight of the body so that muscles may be "freed" to effect joint motion.

Total Motion Muscle Action

This is a product of the entire body. Motion once started is continuous. Movements are di-

vided into components only for descriptive purposes. Total motion embraces everything from pre-skiing "warm-up" exercises to the synchronous muscle actions in linked short swing turns in powder snow.

Unweighting

Unweighting may be done by an up or down motion. In basic technique up unweighting is used primarily because it is slower, more consistent with the student's muscular ability, and therefore safer. Down unweighting is used in advanced technique and racing.

Axial Motion

This refers to motion about the vertical axis of the body. In basic technique counter rotation is taught; but rotation is recognized as an essential turning force in advanced technique.

Edge Control (Angulation)

This is the adjustment of the angle between the skis' running surface and the snow. Basic technique emphasis is placed on leaning out with the upper body; but there are many modifications of this and the use of finer adjustments in the lower body in advanced skiing.

Weight Transfer

This is the movement of weight towards one ski. The ski being broader at the tip than it is in the waist produces immediate turning power when the edged ski is weighted. The bend of the outside knee and ankle is critical for achieving weight transfer. Angulation alone at this point will not produce effective weight transfer to the outside ski. The principle of weight transfer applies whether the beginning skier is going five miles an hour and must transfer 50 pounds of weight to the edge of the ski or whether the racer going much faster requires a mere five pounds of shift.

Leverage (Forward Lean)

This is the effect of the skier's weight before or behind the center of gravity. Back lean applies primarily to advanced ski technique.

Application of Basics

The basic principles are not applied in all phases of all turns. One may visualize the applicability in the demonstrations of the final forms of the American technique or any other technique. The final forms are the progress points in learning to ski and represent the transitional phases in ski technique. These are critical to ski safety.

The Snow Plow

In the snow plow turns and straight running the skier is immediately involved with weight transfer, angulation, and total motion; he is now learning about rhythm in skiing. The snow plow turn is not used as a braking force as it was back in the days of the Oslo technique but rather as a broad based platform to teach safe turning at this level. If one places the inside ski parallel to the outside ski of the individual doing a snow plow turn one will note an ideal body position for a parallel turn.

Traverse

A proper traverse provides the base of operation for all turns. The natural method of standing on an inclined plane is with the uphill ski, knee, hip, and shoulder slightly advanced, with the weight primarily on the lower ski.

Stem Turn

This may be thought of as the link between traverses. An experienced teacher can tell at a glance in watching students perform stem turns whether or not they are able to ski under control (Figure 5).



Figure 5

Forward Side Slip

Ski teaching to this point has dealt with the student who skis on an edged ski to develop a "holding ability" with the mountain. The forward side slipping ability is necessary to teach the student how to release an edge. It involves

a loss of the angulated position with the hips moving out and forward, thus flattening the ski. Once the ski is released the student must keep the center of gravity ahead to prevent the ski from sliding out from under him. It is necessary to acquire the kinesthetic sensation essential to maintain balance in a controlled forward side slip before one can properly ski parallel turns.

Uphill Christie

This is effective in teaching up or down unweighting so that the edge of the ski may be released. The rhythm for powder skiing may be taught at this point. Many skiers fail to learn to initiate a turn with body motion but rather rely on a happenstance of terrain or momentum to unedge the ski so that they may turn. The uphill christie is an excellent mechanism for teaching the initiation of the turn; it is also important for teaching the end phase of a turn, that is, the sinking motion of the lower body. There is a classic debate among ski instructors as to whether the uphill christie has more value in teaching the beginning or the ending phases of a turn. It should, however, be remembered that most skiers can finish a turn once it is started. It is only their lack of ability to initiate a turn at any given moment that might keep them from the delights of powder snow, skiing through gates, etc.

Stem Christie

This has been classically defined as a stem to the fall line and a christie out of the fall line. In contrast to the old *abstemm* days it is considered wise to place the new outside ski in the desired direction of travel and then simply stand on it to produce the turn.

Up unweighting and weight transfer are the prime basic principles involved. The platform may be progressively narrowed as an approach to parallel skiing. Total motion is beautifully obvious when one observes a series of well performed stem christies. As it was in Hannes Schneider's day this turn is still considered by many to be the bulwark of the majority of recreational skiers.

Parallel Turn with the Check

This emphasizes marked flexion of the knee and ankle, angulation, up unweighting, total motion, and counter rotation. The skier sets the platform with down motion which permits him to explosively unweight and initiate the parallel turn. The single feature demonstrated here of being able to set the inside edge of the lower ski as a platform for unweighting for the turn determines the facility with which the maneuver is performed. This is the main feature that separates a *regular* from an *occasional* "parallel turner."

Variations of the parallel, such as short swing (Figure 6), and short swing on a traverse, represent the completion of basic technique. These turns, however, were considered advanced technique a short 10 years ago, when very few skiers could perform them properly. Yet they are cornerstones of today's advanced techniques.



Figure 6

Comments

Today we are a nation of much safer skiers than we were 10 years ago. A survey of the housewives skiing groups, ages 20 to 40, will show many performing parallel turns. This is one of the safest statistical groups in skiing. A methodical approach to ski teaching makes a significant difference in the student's rate of progress and confidence. His enjoyment is greatly enhanced should he be one of the privileged few with the physical ability to ski advanced technique, ice and powder snow. The basic principles may require a little "bending." However, unless the student has methodically acquired a sound basic foundation his chances of safety and technically reaching advanced skiing are markedly diminished.

Patter. Skiing is best when you have lots of white snow and plenty of Blue Cross.—Quoted by Earl Wilson.

The Slowly Moving Finger

The smaller the mammal, the faster the rate of its metabolism; the more rapidly, so to speak, it lives. We might well suppose that while a small mammal doesn't live as long as a large one, it lives more rapidly and more intensely. In some subjective manner, the small mammal might be viewed as living just as long in terms of sensation as does the more sluggish large mammal. As concrete evidence of this difference in metabolism among mammals, consider the heartbeat rate. The following table lists some rough figures for the average number of heartbeats per minute in different types of mammals.

Shrew	1000	Sheep	75
Mouse	550	Man	72
Rat	430	Cow	60
Rabbit	150	Lion	45
Cat	130	Horse	38
Dog	95	Elephant	30
Pig	75	Whale	17

For the fourteen types of animals listed we have the heartbeat rate (approximate) and the maximum age (approximate), and by appropriate multiplications, we can determine the maximum age of each type of creature, not in years but in total heartbeats. The result follows:

Shrew	1,050,000,000	Sheep	600,000,000
Mouse	950,000,000	Lion	830,000,000
Rat	900,000,000	Horse	800,000,000
Rabbit	1,150,000,000	Cow	950,000,000
Cat	1,350,000,000	Elephant	1,200,000,000
Dog	900,000,000	Whale	630,000,000
Pig	800,000,000		

Allowing for the approximate nature of all my figures, I look at this final table through squinting eyes from a distance and come to the following conclusion: A mammal can, at best, live for about a billion heartbeats and when those are done, it is done.

But you'll notice that I have left man out of the table. That's because I want to treat him separately. He lives at the proper speed for his size. His heartbeat rate is about that of other animals of similar weight. It is faster than the heartbeat of larger animals, slower than the heartbeat of smaller animals. Yet his maximum age is 115 years, and that means his maximum number of heartbeats is about 4,350,000,000.

An occasional man can live for over 4 billion heartbeats! In fact, the life expectancy of the American male these days is 2.5 billion heartbeats. Any man who passes the quarter-century mark has gone beyond the billionth heartbeat mark and is still young, with the prime of life ahead.

Why? It is not just that we live longer than other mammals. Measured in heartbeats, we live *four times as long! Why?*

Upon what meat doth this, our species, feed, that we are grown so great? Not even our closest non-human relatives match us in this. If we assume the chimpanzee to have our heartbeat rate and the gorilla to have a slightly slower one, each lives for a maximum of about 1.5 billion heartbeats, which isn't very much out of line for mammals generally. How then do we make it to 4 billion?

What secret in our hearts makes those organs work so much better and last so much longer than any other mammalian heart in existence? Why does the moving finger write so slowly for us, and for us only?*

*Isaac Asimov: Of Time and Space and Other Things, 1965.

Preoperative Preparation of the Skin

SEYMOUR HANDLER, M.D.*

THE PREPARATION OF the skin of the operative site before surgery to prevent surgical wound infection should be effective, simple and inexpensive. An informal survey of operating room nursing supervisors in Minneapolis indicated numerous procedures to prepare the skin, including several with discredited germicides and others using antagonistic agents. The supervisors made a plea for a uniform and effective technique to make their work easier.

Although the preoperative preparation of the skin is important, the patient, operating suite procedure and surgical technique play a larger role in preventing wound infections. The most perfect degerming of the skin will not prevent infection if the surgeon leaves devitalized tissue and blood-filled spaces in the wound. If surgical and operating room suite technique are good, then a good skin preparation can reduce wound infection to an extremely low level.

First, what are we trying to accomplish? Since it is impossible to sterilize the skin without destroying it, we hope to make it as germ-free as possible with suitable cleansing and antisepsis. The skin through which the incision is made has both a resident and a transient bacterial flora.[1] Resident bacteria are either on the surface in the keratin layer or in the hair follicles and sebaceous glands. Most resident bacteria are nonpathogens, but potential pathogens are almost always present. Transient bacteria are present on the surface and are constantly changing in quantity or type depending on exposure of the patient, washing and location on the body. Thus the superficial bacteria are readily killed by suitable antiseptics if sebum and debris are removed by cleansing agents.

Cleansing the Skin

The skin may be prepared for surgery in three steps:

1. Use a soap or detergent to remove the dirt and water-insoluble material to prepare the operative site for the germicide. Repeated cleansing contributes to effectiveness by removing more sebum.
2. Leave some residual antibacterial layer on the skin, so that as the deeper resident flora rises to the surface with sebum flow, the bacteria will be inhibited from multiplying.
3. Apply an effective germicide to kill *all* superficial bacteria, both resident and transient. An ideal vehicle for the germicide should be a fat solvent to allow greater penetration into the skin.

Germicides

In addition to a soap or detergent, agents used as germicides to achieve the above procedure are (1) organic mercurials, (2) quaternary ammonium compounds, (3) alcohol, (4) hexachlorophene, and (5) iodine. A brief discussion of each of these is in order to consider their merits and deficiencies.

Organic Mercurials

The organic mercurials (metaphen, mercurochrome, merthiolate, etc.) have enjoyed wide use as skin disinfectants since early in the century. Their major shortcoming is that they are bacteriostatic rather than bactericidal, so that they can not fulfill the requirement of killing all superficial skin bacteria on contact. Figure 1[1]

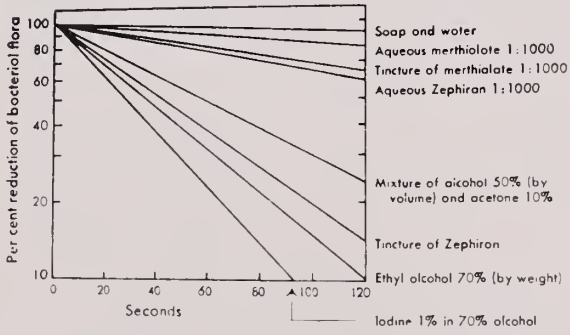


Fig. 1—Relation of time and reduction of bacteria by various skin antiseptics.[1]

*Associate Pathologist, North Memorial Hospital, Minneapolis, Minnesota.

indicates that merthiolate is little better than soap and water in reducing skin bacteria and distinctly inferior to other available agents. Placing merthiolate in an alcohol tincture improves performance, but alcohol alone would do as well. The inability of organic mercurials to be bactericidal and the availability of better agents strongly suggest that this group should be abandoned as skin antiseptics.

Further examination of Figure 1 should dispel the notion that soap and water alone are adequate disinfectants of the skin. The sole function of soap or detergents should be to remove dirt and oily substances to allow effective germicidal agents to work. Surgeons who insist on a soap scrub alone for preparation are depending too much on their own surgical skill and the patient's antibacterial defenses to prevent wound infection.

Quaternary Ammonium Compounds

The quaternary ammonium surface active disinfectants (Quats) achieved great popularity as medical disinfectants after the Second World War. The most popular, benzalkonium chloride (Zephiran), is listed in the United States Pharmacopeia. Although the group has significant in-vitro bactericidal activity, the cationic chemical nature of Zephiran greatly limits its usefulness in clinical practice. In the presence of anionic compounds, particularly soaps or detergents, an antagonistic chemical reaction inactivates the antiseptic. Since most preoperative skin preparation begins with a soap scrub, residual soap essentially inactivates the germicidal activity of Zephiran. Figure 2[2] demonstrates that the sequence of soap followed by ordinary rinsing and Zephiran is no

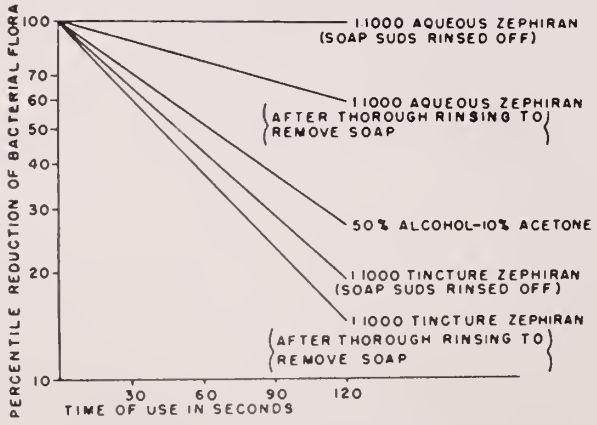


Fig 2—Comparison of benzalkonium chloride (Zephiran) in various situations involving soap.[2]

better than soap alone. Zephiran in an alcohol tincture is better, but the difference is due solely to the alcohol.

The inactivation of cationic Quats by anionic soaps has been known since 1935[3] and was emphasized in the American literature[4] in 1950. Despite this knowledge, a survey of hospital disinfecting practices in 1950[5] indicated widespread use of combinations of soap and Quats. Our informal survey in 1965 indicated similar practice. There may be uses for benzalkonium chloride as an antiseptic in some clinical situations, but certainly not for preoperative antisepsis of the skin.

Further limitation of the clinical usefulness of the Quats have been reported[6,7] in Pseudomonas infections attributed to the organisms growing in solutions of benzalkonium chloride. Serious infections occurred from cotton pledgets stored in solutions of benzalkonium chloride. Pseudomonas apparently thrives in this environment.

Alcohol

Ethyl or isopropyl alcohol is an effective bactericidal antiseptic on the skin in concentrations between 70 and 95 per cent. The decreasing popularity of these very effective and inexpensive skin degerming agents is attributed to the enthusiastic salesmanship of the manufacturers of Quats and iodophores. Evidence in the literature adequately supports the use of 70% ethyl alcohol as a skin disinfectant, and yet the survey[8] indicates decreasing popularity.

Hexachlorophene

Hexachlorophene is a bacteriostatic agent from the family of chloride-substituted bisphenols. The popularity it achieved in the 1950s stemmed from the belief that the preoperative hand scrub of the surgeon could be reduced in time by scrubbing with a soap containing hexachlorophene. The amount of residual antibacterial action of the hexachlorophene has been criticized[9] as distinctly overstated by both manufacturer and user. The features of hexachlorophene important to our consideration are as follows:

Hexachlorophene has bacteriostatic action only. Therefore it can not kill all bacteria on the skin at the time of surgery. The use of a soap incorporating hexachlorophene as the sole

preparation of the surgical skin is in error.

Hexachlorophene is less effective against gram-negative than gram-positive bacteria.[10] This becomes increasingly important in parts of the body—perineum, inguinal and lower abdomen — where coliforms are a constant member of the resident flora. The increasing problem of Pseudomonas and other gram-negative bacteria as a source of wound infection and sepsis further compounds this deficiency.

The effectiveness of hexachlorophene is not affected by soap and this led to its combination with various soaps and detergents.

Hexachlorophene is insoluble in water and soluble in fats. This feature probably accounts for its ability to remain in the superficial part of the skin for some time after its application and residual action. Very frequent applications are required for significant residual bacteriostatic action,[9] and a single application at the time of surgery does nothing to affect the skin flora.

Iodine

Iodine has enjoyed a deserved reputation most of the century as the almost nearly perfect antiseptic and is probably the most effective antiseptic relative to toxicity of any agent. It rapidly kills both gram-negative and positive bacteria in equal concentration, and is lethal to fungi, tubercle bacilli and viruses. Its bactericidal efficiency[11] is directly related to the concentration of free iodine. It is effective in the presence of soap, hard water and organic matter.

The decline in usage of iodine relates to the irritating action of the older Iodine Tincture. The old Tincture with 7% free iodine was too strong and burned enough patients to convince surgeons to look to safer skin antiseptics. Even when the U.S.P. Iodine Tincture was changed in 1947 to 2% iodine, the popularity of iodine did not return. Recent work[12] has demonstrated that 1% iodine in alcohol (Figure 1) offers excellent bactericidal action and very little, if any, of the irritating properties of the former stronger solution.

Because of the unhappy reputation of iodine in the days of the strong Tincture, pharmaceutical manufacturers developed a family of iodophores, iodine complexed with organic molecules. Iodophores are designed to "carry" iodine and release it as "available" iodine in a use situation. The complexing of iodine in a carrier molecule is supposed to "detoxify" it and prevent it from burning the skin. Are these claims true? Work by King and Price[12] using the serial-basin scrub technique indicates that a group of iodophores (Virac, Ioprep and Betadine) were distinctly inferior (Figure 3) to 1% iodine in 70% alcohol and only slightly better than Ivory soap. Their work reasonably questions the "availability" of free iodine in iodophores. Gershenfeld[11] has shown that the bactericidal action of iodine is related to the concentration of free iodine. So would this not suggest that the relatively non-irritating properties of the iodophores and their inability to kill bacteria in 1% solution are related to the same fact—that the iodine is not "available." The enthusiastic support of the iodophores in recent years may be akin to the prior support of the Quats, a group of agents now not recommended as clinical skin antiseptics.

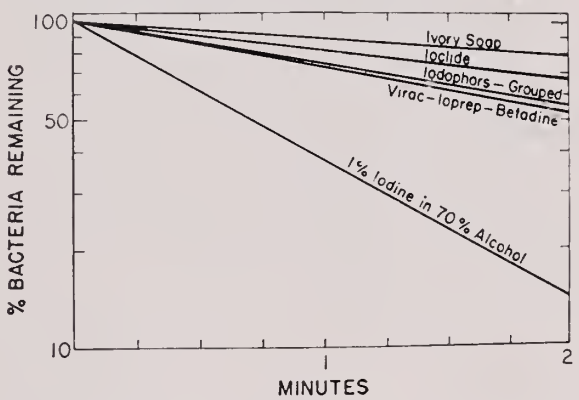


Fig. 3—Comparison of iodophores with 1% iodine in 70% alcohol.[12]

Procedures of Choice

The recommended procedure of preoperative preparation of the skin varies with the clinical situation. If the patient is cooperative and five days are available prior to surgery:

1. Scrub with pHisoHex daily for five days and in the operating room.
2. Apply 1% iodine in 70% ethyl alcohol to the skin once and allow to dry.

If the situation is an emergency or if patient cooperation and five days are not present.

1. Scrub with Phisoderm (or pHisoHex) in the operating room.

2. Apply 1% iodine in 70% ethyl alcohol twice and allow to dry.

The latter procedure has been practiced with no increase in wound infection rate and no documented iodine irritations for five years. King[13] has had additional extensive experience with this technique with similar good results. His series includes many cases in which the incision site prepared with 1% iodine in alcohol has been covered by plaster casts, with no untoward reactions occurring.

Conclusion

The commonly used skin antiseptics have been reviewed and their merits and deficiencies detailed. Proper skin preparation consists of cleansing with a soap or detergent to remove dirt and oily substances, followed by application of a bactericidal antiseptic. The organic mercurials, quaternary ammonium compounds and hexachlorophene above are unsuitable preoperative skin antiseptics; either 1% iodine in 70% alcohol or 70% alcohol is an effective skin antiseptic. A recommended procedure includes cleansing of the skin with Phisoderm and application of 1% iodine in 70% alcohol. If time and patient cooperation are present, daily scrubbing with a hexachlorophene soap may contribute residual antibacterial action to the above.

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The Biology of Social Life

The first law of the herd is "Thou shalt not." Just as the development of the higher nerve centres checks instinctive activities, so the development of communal life must restrict the freedom of the individual. Man has not found this easy. Philosophers may lament this, theologians may attribute it to original sin, but the biologist will remember that the cells of which he is composed did not find it easy to sink their individuality in that of the organism. A clever woman once said to me of her son: "He hasn't fused his ancestors yet." It was profoundly true.*

*Sir Walter Langdon-Brown: Thus We Are Men, 1969.

It is with narrow-souled people as with narrow-necked bottles: the less they have in them, the more noise they make in pouring it out.—Jonathan Swift

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Be not simply good; be good for something.—Henry David Thoreau

Snowmobiling Injuries

RICHARD A. FINK, M.D.* and JAMES J. MONGE', M.D.†

In the past five years snowmobiling has become one of the fastest growing winter activities in the northern United States. It has been estimated that 397,000 snowmobiles were sold from 1962 through the spring of 1968, and sales for the 1968-69 season were expected to reach 250,000.[1] Despite this tremendous growth, the medical literature contains only a few papers describing injuries sustained in this sport[2,3,4,5,6,7] The purpose of this paper is to recount such injuries as seen in one northern community.

Material and Methods

This study was conducted in the emergency rooms of St. Mary's and St. Luke's Hospitals, Duluth, Minnesota, from November 26, 1968, through March 18, 1969. All patients injured in accidents involving snowmobiles were given a questionaire to answer while in the emergency room. This questionaire was designed to determine the personal characteristics of the injured person, the nature of the equipment being used, and the circumstances in which the accident occurred. The attending physician recorded the type of injury on the same form. This study is based on these questionaires. Follow-up data was obtained only on patients who were hospitalized because their general condition was endangered.

Results

A total of 171 patients, involved in 169 separate accidents, were seen during the 111 days during which the study was conducted. They accounted for 2.17 per cent of the total of 7,802 patients treated in the emergency rooms during this period.



Figure 1

TABLE 1
Snowmobile Injuries

Mechanisms of Injury	
Struck part of machine while on rough terrain (14 of 46 occurred when clutch was struck)	46
Capsize of vehicle	32
Thrown from vehicle	18
Struck fixed object	17
Collision with another snowmobile	8
Snowmobile driven over precipice	7
Foot caught in track	4
Thrown off and struck by following snowmobile	4
Collision with moving auto	2
Collision with fence	1
Miscellaneous	17
Mechanisms not specific	15

TABLE 2
Snowmobile Injuries

Types of Injury		
Soft tissue injuries not associated with any more serious injury	98	59%
Ligamentous and cartilaginous injuries	30	18%
Fractures	32	19%
Dislocations	3	2%
Visceral injuries	6	4%

*1025 Fourth Avenue, Southeast, Rochester, Minnesota.
†Duluth Clinic, Duluth.

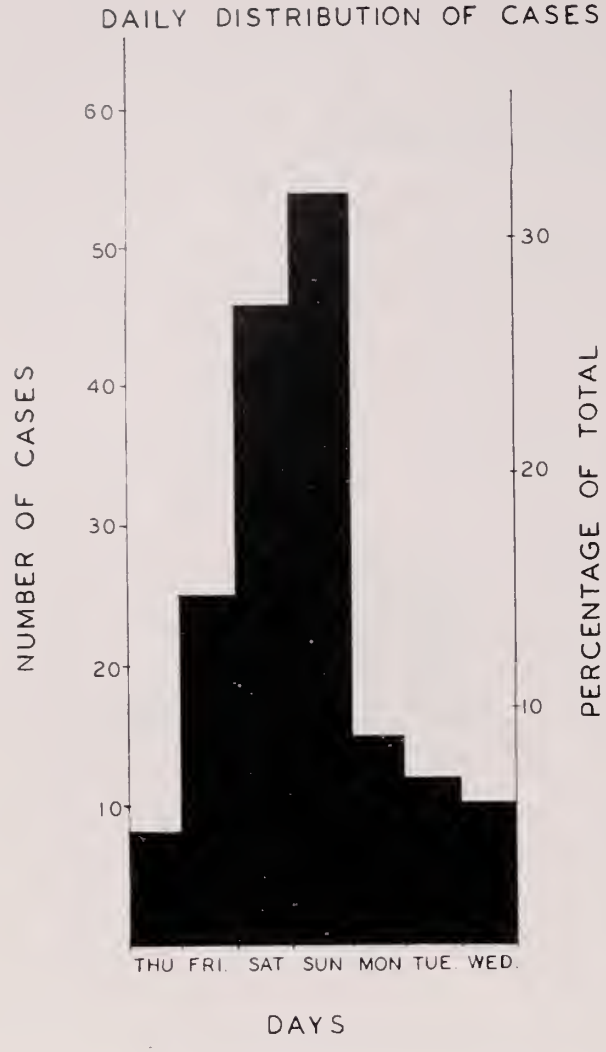


Figure 2

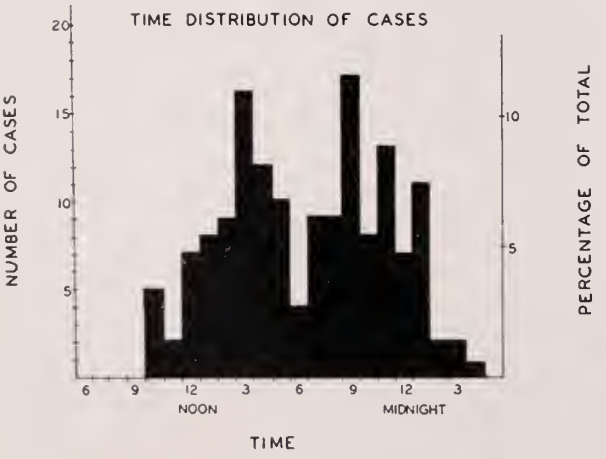


Figure 3

Distribution

The median age of the patients was 31.0 years; 92% were less than 45 years old (Figure 1). Males accounted for 80% of the injured. There was a significantly higher incidence of injury to drivers compared to passengers riding snowmobiles. However, in accidents involving snowmobiles that were towing sleds there was a greater incidence of injury to passengers on the sleds than to the drivers.

Mechanisms and Types of Injury

The mechanisms of injury are shown in Table 1; the types of injuries are detailed in Table 2. Twenty-seven cases (16%) were severe enough to require hospitalization. There was one death in the series.

Case Histories

Unseen Objects

This case is presented because it represents a common cause of serious injury to snowmobilers who strike unseen objects. A 25-year-old man with over 50 hours of experi-

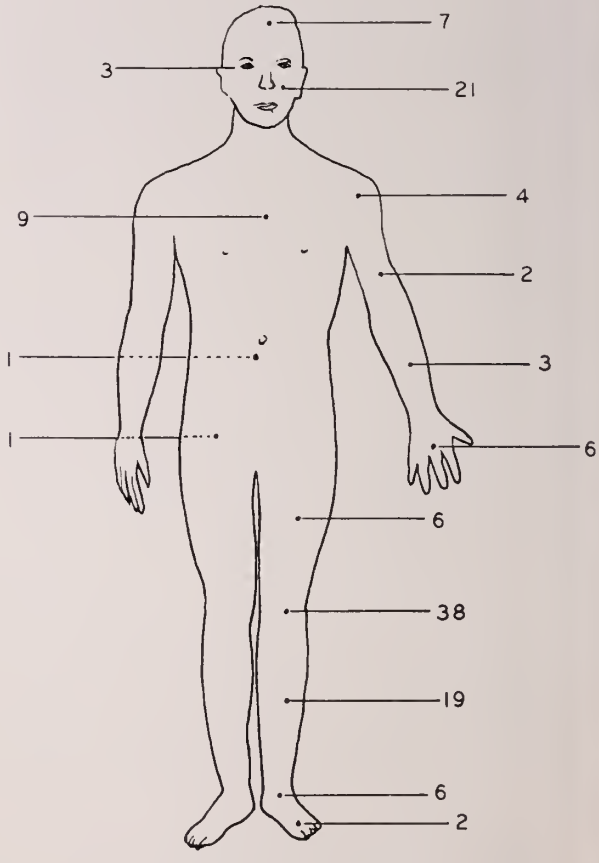


Figure. 4—Distribution of soft tissue injuries.

ence was driving his 24-horsepower snowmobile at 10:15 P.M. when, without seeing it ahead of time, he ran into a barbed-wire fence. One of the wires struck him in the mouth and produced multiple, deep, jagged lacerations of the lips, mouth and cheeks. These injuries required extensive and multiple plastic surgical procedures under general anesthesia.

Fatal Injury

This case represents the one death in the series. A 55-year-old man, accompanied by his 48-year-old wife, was driving his snowmobile along with a group of other snowmobilers at 1:30 A.M. The exact mechanism is not clear, but it is thought that one of the leading machines lost a ski which flew into the air and struck the man in the head, causing his snowmobile to go out of control and overturn. The man's wife suffered a concussion and an orbital rim fracture. The man himself had a basilar skull fracture and extensive injury to his anterior skull with severe disruption of the frontal and temporal lobes of the brain. He died seven days after the accident.

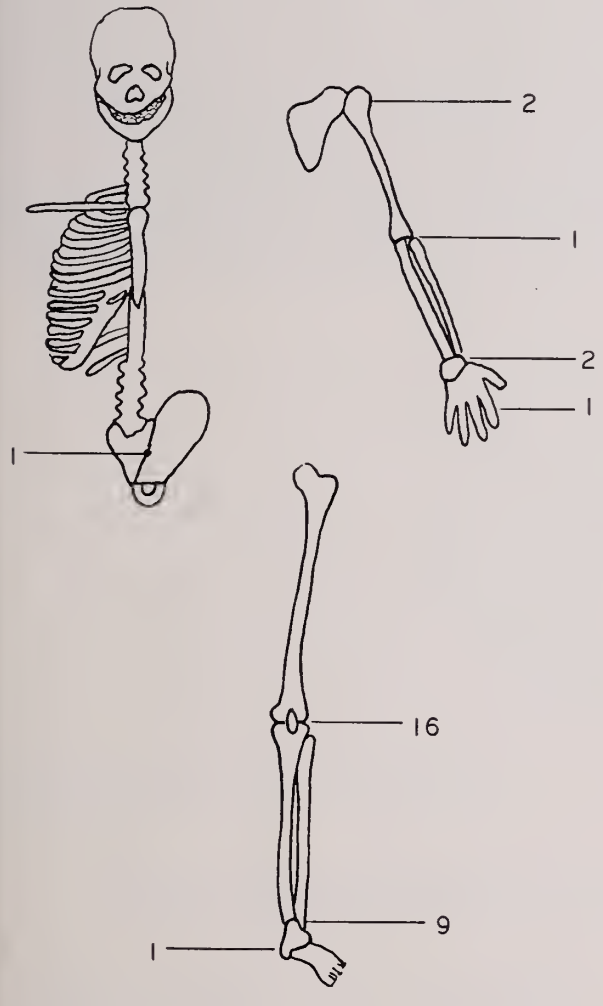


Fig. 5.—Distribution of ligamentous and cartilaginous injuries.

Head Injury

This case involves a second very serious head injury. A 25-year-old man with 40 to 50 hours experience was driving an 18-horsepower snowmobile at about 6:00 P.M. The road on which he was driving was described as hard and glossy, making steering very difficult. While rounding a curve at 30 miles per hour he lost control of his vehicle and slid head-on into an automobile parked on the outside of the turn. He suffered an epidural hematoma and a fractured femur. Despite surgical evacuation of the hematoma he sustained extensive, irreversible cerebral damage. He remains in a purely vegetative state in a nursing home at the time of this writing nine months after his initial injury.

Discussion

Duluth lent itself well to this study for a number of reasons. It is estimated that there are over 5,000 snowmobiles among the 127,000 residents in the Duluth metropolitan area.[8] The region receives enough snowfall to allow snowmobiling continuously throughout the four winter months. During the winter of 1968-69 Duluth had a total of over 110 inches of snow which provided excellent snowmobiling conditions throughout the period of this study.

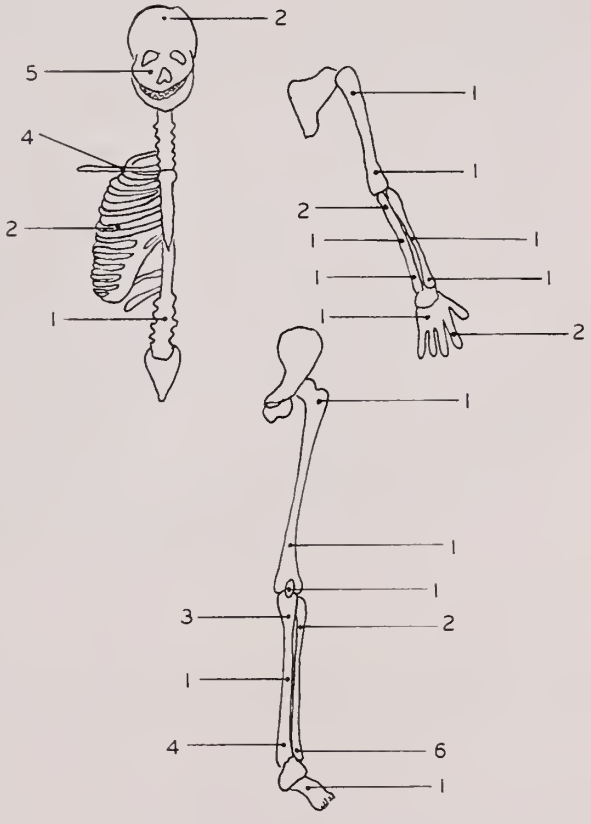


Fig 6—Distribution of fractures.

Incidence and seriousness of injury may possibly be related to the speeds of the vehicles. Many operators appear not to realize the danger in driving the light vehicles at high speed and the possibility of serious injury; others engage in reckless driving and stunting. From our clinical observation we believe that alcohol consumption is a significant factor; though only 22% admitted alcohol ingestion prior to the accident, 14% did not answer the question, and 64% denied it.

Snowmobiling has become a very rapidly growing pastime, and if the sport continues to boom, then it can be expected that the number of related injuries will also increase.

Summary

Of 171 cases of snowmobile injuries, most occurred when the victim was thrown against the snowmobile structure or off the vehicle entirely, or when the machine overturned or struck a fixed object. Fifty-nine per cent of the victims suffered only simple soft tissue injuries; the remainder had ligamentous and cartilaginous injury, fractures, dislocations, and visceral injuries. Lower extremity injuries were most common. Five patients had brain injuries.

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Ugly Duckling Genius

The theme of isolation, of being different constantly creeps into Andersen's work, and with reason. Clara Schumann called him the ugliest man alive; a noted Danish sculptor remarked on the strange shape of his head.

In the opinion of Dr. Leo M. Davidoff and others, the long arms, enlarged hands and feet, prognathism, and prominent orbital ridges raise the suspicion of acromegaly. Notes Dr. Davidoff: "I would say that the high soprano voice up to the age of fifteen, and his failure to shave up to the age of twenty-three, would indicate that a pituitary disturbance existed prior to the development of the particular change in this gland that gave rise to his eventual acromegalic appearance."

He suffered from toothache all his life, complained of a variety of illnesses; in later life he developed a full-blown hypochondria. His journal is full of references to "coagulated blood, rheumatism of the nose, buzzing in the jugular veins." He feared that he might have swallowed glass, taken poison instead of medicine, contracted glanders from a horse's spittle. Wrote he: "The mosquitoes bit me; I may get apoplexy."

His journal verifies his fear of insanity, his suicidal thoughts, his desire for medical help. "I ought to talk to a doctor . . . one who could enlighten my sick mind." He was plagued by nightmares in which his throat and mouth were filled with hair.*

*Felix Marti-Ibanez: The Pageant of Medicine, 1960.



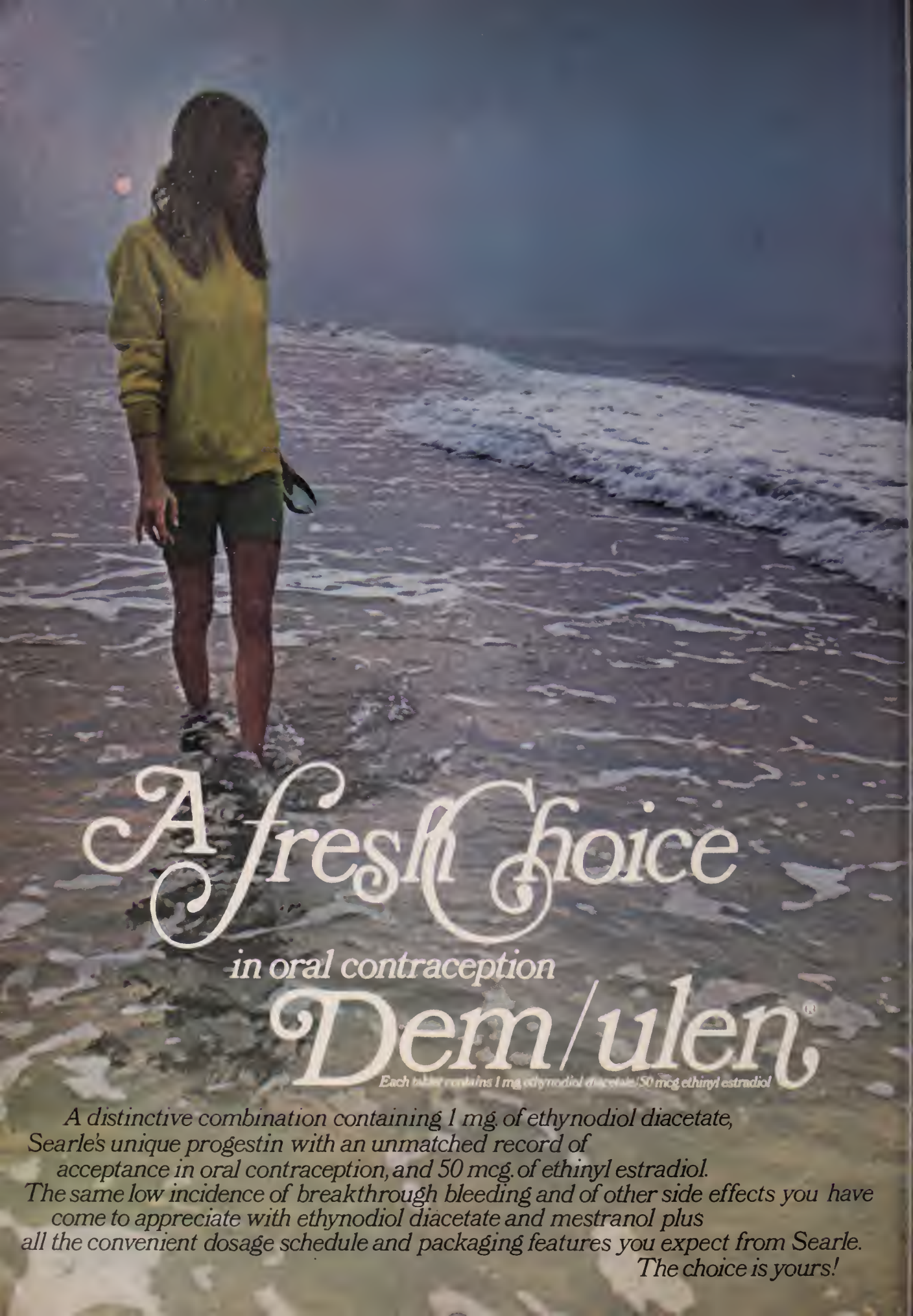
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Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.



Indication—Demulen is indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Demulen. Therefore, if such tests are abnormal in a patient taking Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Demulen may mask the onset of the climacteric. The pathologist should be advised of Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions; neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

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Editorials

Skiing

Teach inside the Limits

Ever since the first skier slid down a mountain there has been controversy over style of skiing, though all teaching systems agree that the upright position, not the horizontal, should prevail.

The steepness and length of the slope, condition of the snow, visibility, moguls, traffic congestion, and temperature are factors which control the instructor's teaching methods. Any misfortune that can happen to an individual while skiing can also occur in a class. Safety in skiing is a direct product of the instructor who must set for himself and his pupils certain limits which serve to control or contend with the multiplicity of injuries that may occur: collisions, lift accidents, avalanches, heart attacks, mental breakdowns, frostbite, sunburn, snow blindness, bruised and blistered feet, altercations, drownings and miscarriages. Pupils have skied off the bridge into the river and lessons have been refused to hardy distaff skiers who thought that a week of skiing in class might be relaxing before making the last run to the maternity ward.

Safe operation of a ski school starts with the school administrator's separating his pupils into classes according to their skiing ability, physical strength, age and enthusiasm, in order to control and check the instructor who is tempted to push his class into speed and difficult maneuvers which he cannot handle.

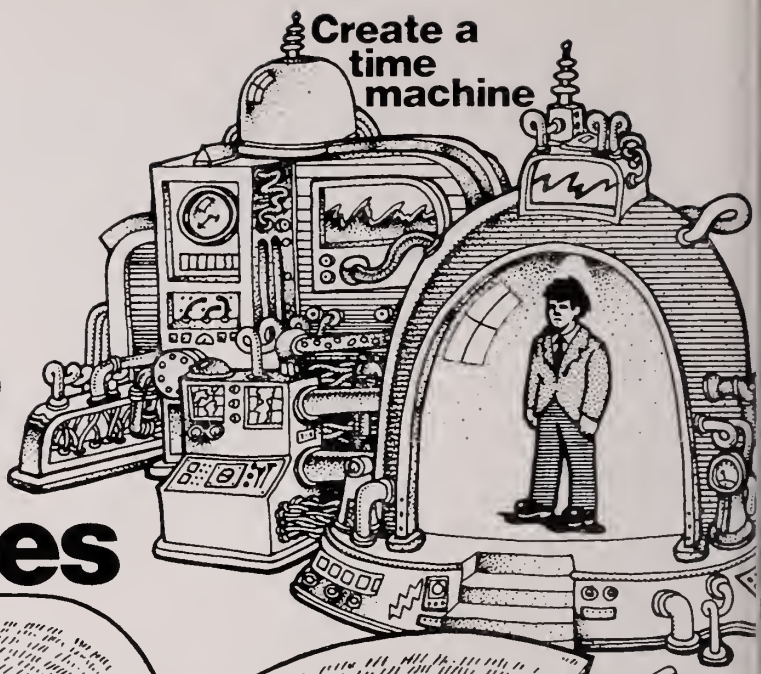
Before starting his session the instructor should allow his pupils to warm up before encouraging them to try some unfamiliar movement, as muscles do not respond well when a pupil is apprehensive, nervous or frightened. Falling while under tension may invite injury whereas a relaxed fall might even be fun.

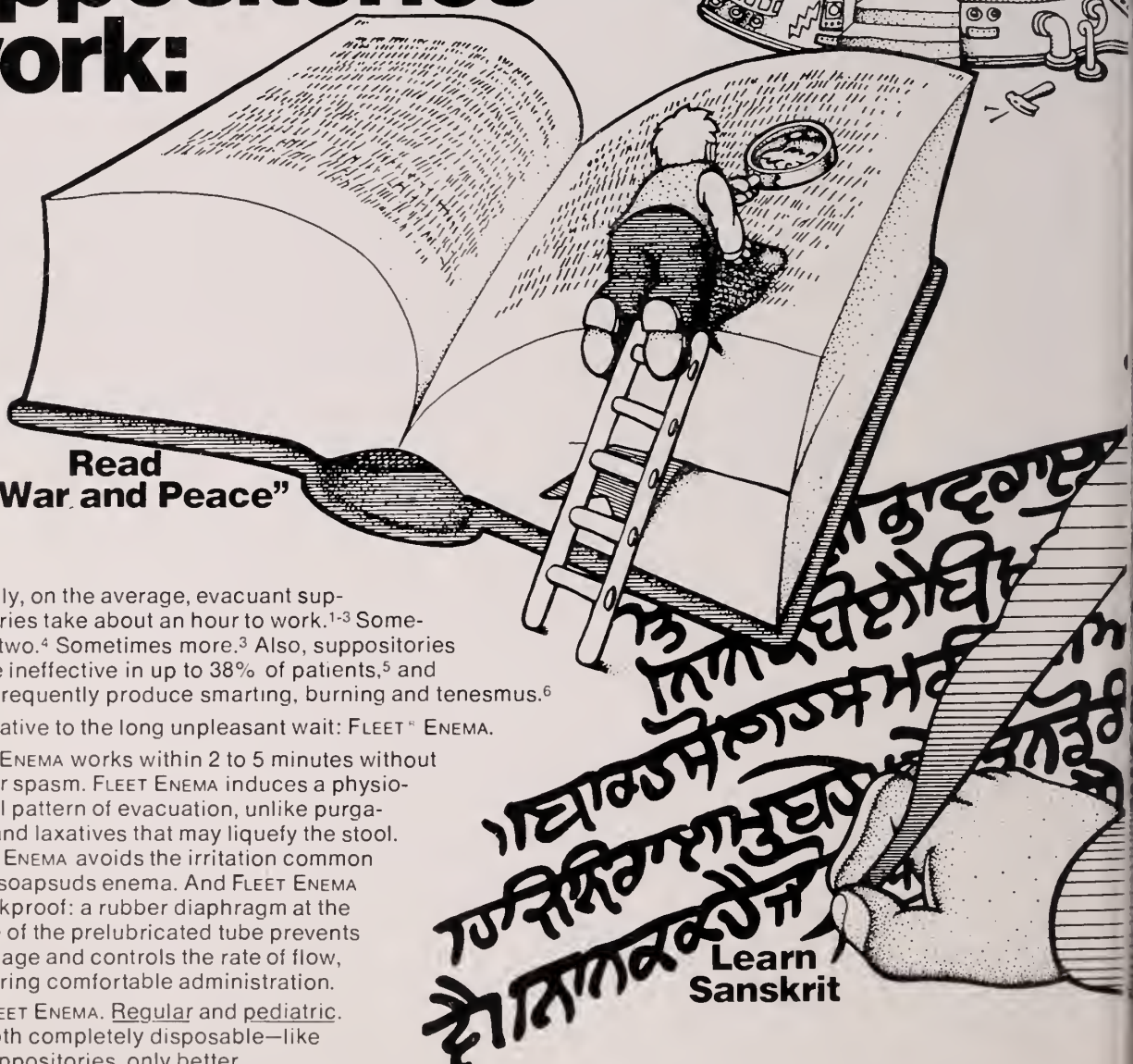
Deep snow in the spring and the uncertain nature of the terrain always provide the avalanche problem. A seemingly harmless fall on a steep slope may result in serious injury if the sliding skier picks up speed which he cannot control. Most ski clothing, warmup pants and sealskin jackets are almost as fast as the modern ski. A sealskin jacket has been known to set a record at Sun Valley when a lady skier fell near the top of Canyon and came to a stop near the top of River Run, a quarter of a mile and several hundred vertical feet later. Fortunately she was not hurt as she arrived only seconds behind one of her skis.

Paul Ramlow*

*Sun Valley, Idaho.

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References: 1. Blumberg, N.: Med Times 91:45, Jan., 1963. 2. Sweeney, W. J., III: Amer J Obstet Gynec 85:908, Apr. 1, 1963. 3. Weinsaft, P.: J Amer Geriat Soc 12:295, Mar., 1964. 4. Baydoun, A. B.: Amer J Obstet Gynec 85.905, Apr. 1, 1963. 5. Feder, I. A., Flores, A. and Weiss, J.: Amer J Gastroent 33:366, Mar., 1960. 6. Smith, J. J. and Schwartz, E. D.: Western J Surg 72:177, May-June, 1964

The Editor's Soliloquy

A Song in the Soul

In this issue manuscripts relative to winter sports have been introduced because of the ever-increasing participation in a sport which, to the uninitiated skeptic, seems hazardous even in its esoteric vernacular. To one acrophobe the instructor's introductory reference to the "fall line" was just enough to make her cancel out on the ski-week class lessons. She thought that "downhill" would have been sufficient for clarity; but "fall line," with its ominous connotation of a vertiginous tumble down a steep grade, produced an abrupt and acute syncope, and she'd "be darned" if anyone was going to hypnotize her into hurtling out of control down that mountainous slope.

"Bend zee knees, stand up straight, spread zee legs, knees together, lean downhill, uphill christie, rotate hips, lead with zee knees, uphill ski ahead, weight on zee downhill, forward side slip, thrust with zee heels, down upweight, up unweight," were more than sufficient to make the novitiate yell in utter confusion: "Make up your mind!"

Like chess and golf, skiing is an addictive sport. After a half dozen trials one abandons the thought of ever becoming a skier or becomes "hooked" for life.

True, proficiency is not quickly or easily acquired. For the rewards to be worth the effort in this Olympian sport, expertise in skiing requires persistent practice and demands resolute endurance. The participant is invited to exult in observing and admiring grace and power in a handsome body in swift motion, demonstrating a consummate fusion of agility and coordination—such as no other sport can exhibit. The body becomes no longer an incubus or liability of bone, blood and tissue, but a superbly mobile and adroit instrument for transcending mundane inertia and limitation. Though you may ski to win, you approve him who does it better and you strive without envy or animosity to equal or even surpass his perfection. All in the spirit of that fine camaraderie so endemic to the elite fraternity of skiers!

What's more: skiing initiates and fosters an abiding love of Nature. In the splendor of a white winter background one skims over snowy-surfaced hills and valleys, soaring through ambient air with smooth speed that exhilarates the body, tranquilizes the nerves, and exalts the spirit. An epic performance in a lyric setting!

Skiing is an ache in the bones and a song in the soul.

Carl O. Rice, M.D.

Old Doc Hess says: If you feel all tied up in knots try sitting on the purr button instead of on the panic button.—C.O.R.

Without going you can get to nowhere; you can complete nothing without doing.
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The cure for all this world's distress is found in simple friendliness.—John Jarvis Holden

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Physical and Psychological Dependence: Physical and psychological dependence rarely reported. If withdrawal symptoms do occur they may resemble those associated with withdrawal of barbiturates and should be treated in the same fashion. Use caution in administering to individuals known to be addiction-prone or those whose history suggests they may increase the dosage on their own initiative. Repeat prescriptions should be under adequate medical supervision.
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ADVERSE REACTIONS: At recommended dosages, there have been rare occurrences of morning drowsiness, dizziness, mild to moderate gastric upset (including diarrhea, esophagitis, nausea and vomiting), headache, paradoxical excitation and skin rash. There have been a very few isolated reports of neutropenia and thrombocytopenia; however, the evidence does not establish that these reactions are related to the drug.

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The Paramedical

When I find the AMA advocating the use of "paramedical personnel" for care of the patient I feel that it is time for me to recognize that the "old order" has passed, whether for good or for ill, and that my time for "the old rockin' chair" has come; possibly it came some time ago but I did not clearly recognize the fact.

I got a certain wry amusement from the laudatory article in the JAMA on Russian medicine where actual patient care is in the hands mostly of good women with a little practical instruction in the techniques of psychosomatic medicine while those with doctorial degrees are able to spend their time more usefully in basic laboratory research. I learned that, although the general practitioner is paid less than common labor, possible openings in the medical schools are grossly over-applied for. Evidently the Russians are truly dedicated individuals, free of the taint of commercialism that has sullied our doctors in the USA.

Henry L. Williams, M.D.
West St. Paul, Minnesota

Australia Antigen

Australia antigen is definitely associated with hepatitis and appears to be responsible for the type of hepatitis previously known as serum hepatitis. A prolonged incubation form of hepatitis is also caused by orally ingested material which contains Australia antigen. The classical infectious hepatitis with a short incubation period is not as yet associated with Australia antigen.

At the American Gastroenterological Association course on hepatitis in Aspen, Colorado, in August, 1970, Dr. Alfred M. Prince related his experience with testing blood to be used for transfusions for the presence of Australia antigen. Testing was done by immuno-osmo-electrophoresis, a technique which may be accomplished within two hours. Testing resulted in a decrease of ⅓ in the incidence of hepatitis for single unit transfusions. From a conversation with Dr. Prince, I learned that the New York City Red Cross is now screening all units of blood for Australia antigen. Others at the course mentioned that uniform testing of all blood for Australia antigen is now being done in Los Angeles County Hospital and Methodist Hospital in Dallas, Texas.

Certainly, testing blood for Australia antigen will not eliminate all transfusion hepatitis, but if it will eliminate ⅓ of the cases, it will be worthwhile. It would be of great interest to hear further data on this subject from those most concerned with blood banking in Minnesota, namely: What is the incidence of transfusion-associated hepatitis in Minnesota? What would the testing of blood for Australia antigen add to the cost per unit? Is any blood being tested for Australia antigen in the state? What method offers the greatest promise?

Also, at the Aspen post-graduate course, we heard the increasing incidence of hepatitis associated with hippie drug abuse in Boston well documented by Dr. George F. Grady. In large part, this is an Australia antigen-associated disease. The increasing drug abuse among young people and its association with Australia antigen antigenemia add impetus to routine screening for Australia antigen in our blood banks.

J. N. Mork, M.D.
Worthington, Minnesota


Gone with the wind

The gas/acid group of disorders

"The two most common complaints referable to the upper gastrointestinal tract for which patients seek medical relief are hyperacidity and 'gas.' The two often occur together."*

Frees captured gas...neutralizes free acid

SILAIN-GEL Tablets and Liquid are separate formulas designed to provide equivalent dual-action symptomatic relief. Both dosage forms contain simethicone which effectively frees trapped gas, enabling the patient to eliminate it. Magnesium hydroxide in both assures a rapid rise in pH for prompt relief of hyperacidity. The special co-dried aluminum hydroxide/magnesium carbonate gel in the tablets assures the same rapid and uniform reaction rate as the liquid. Thus, both medications achieve prompt and prolonged neutralization of free acid *plus* prompt relief from the pain and pressure of trapped gas.

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when the patient prefers the convenience of a tablet, select
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Also available for the patient who needs an antifrothicant/antiflatulent agent only: **Silain®** (simethicone) Tablets

Slanger, A.: Med. Times *94*:150 (Feb.) 1966.

Announcing the "Antgasid"

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Tablets: simethicone plus aluminum hydroxide/magnesium carbonate co-dried gel and magnesium hydroxide
Liquid: simethicone plus aluminum hydroxide and magnesium hydroxide
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The actions of the official Tincture and Extract of Belladonna result chiefly from their Atropine content . . . conclude Goodman and Gilman

THE PHARMACOLOGICAL BASIS OF THERAPEUTICS
3rd Edition, page 522



ANTROCOL®

Antrocol provides the prompt, predictable antisecretory action of the belladonna alkaloid, atropine, fortified with sedation and blended with Bensulfoid, contributing to even absorption.



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Caution: Federal law prohibits dispensing without prescription.

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Contraindicated in glaucoma. Use cautiously in prostatic hypertrophy. Side-effects of toxic dose of atropine: flushing, dryness of mouth, cycloplegia, tachycardia and urinary retention.

DOSAGE: One tablet or capsule after each meal to correct emotional stress and normalize gastric secretions. In treating peptic ulcer, doses at regular intervals up to eight (8) tablets or capsules per day to provide the proper gastric titer for healing. After ulcer has healed, one tablet or capsule after each meal to maintain a titer unfavorable to recurrence.

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Tepanil® Ten-tab

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(diethylpropion hydrochloride)

works on the appetite not on the 'nerves'

When girth gets out of control, TEPANIL can provide sound support for the weight control program you recommend. TEPANIL reduces the appetite—patients enjoy food but eat less. Weight loss is significant—gradual—yet there is a relatively low incidence of CNS stimulation.

Controindications: Concurrently with MAO inhibitors, in patients hypersensitive to this drug; in emotionally unstable patients susceptible to drug abuse.

Warning: Although generally safer than the amphetamines, use with great caution in patients with severe hypertension or severe cardiovascular disease. Do not use during first trimester of pregnancy unless potential benefits outweigh potential risks.

Adverse Reactions: Rarely severe enough to require discontinuation of therapy, unpleasant symptoms with diethylpropion hydrochloride have been reported to occur in relatively low incidence. As is characteristic of sympathomimetic agents, it may occasionally cause *CNS effects* such as insomnia, nervousness, dizziness, anxiety, and jitteriness. In contrast, CNS depression has been reported. In a few epileptics an increase in convulsive episodes has been reported. *Sympathomimetic cardiovascular effects* reported include ones such as tachycardia, precordial pain, arrhythmia, palpitation, and increased blood pressure. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride; this was an isolated experience, which has not been reported by others. *Allergic phenomena* reported include such conditions as rash, urticaria, ecchymosis, and erythema. *Gastraintestinal effects* such as diarrhea, constipation, nausea, vomiting, and abdominal discomfort have been reported. Specific reports on the hematopoietic system include two each of bone marrow depression, agranulocytosis, and leukopenia. A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dry mouth, headache, dyspnea, menstrual upset, hair loss, muscle pain, decreased libido, dysuria, and polyuria.

Convenience of two dosage forms: TEPANIL Ten-tab tablets: One 75 mg. tablet daily, swallowed whole, in midmorning (10 a.m.); TEPANIL: One 25 mg. tablet three times daily, one hour before meals. If desired, an additional tablet may be given in midevening to overcome night hunger. Use in children under 12 years of age is not recommended.

T-006A / 1/70 / U.S. PATENT NO. 3,001,910

THE NATIONAL DRUG COMPANY
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Painful night leg cramps...

unwelcome bedfellow for any patient– including those with arthritis, diabetes or PVD

One thing patients can sleep without, particularly patients with chronic disease conditions such as arthritis, diabetes or PVD, is painful night leg cramps. Although seldom the presenting complaint, night leg cramps can tie your patients up in painful knots. Now, just one tablet of QUINAMM at bedtime can usually bring an end to shattered sleep and needless suffering. Your patients will sleep restfully—gratefully—with QUINAMM, specific therapy to prevent painful night leg cramps.

Prescribing Information—Composition: Each white, beveled, compressed tablet contains: Quinine sulfate, 260 mg., Aminophylline, 195 mg. **Indications:** For the prevention and treatment of nocturnal and recumbency leg muscle cramps, including those associated with arthritis, diabetes, varicose veins, thrombophlebitis, arteriosclerosis and static foot deformities. **Contraindications:** QUINAMM is contraindicated in pregnancy because of its quinine content. **Precautions/Adverse Reactions:** Aminophylline may produce intestinal cramps in some instances, and quinine may produce symptoms of cinchonism, such as tinnitus, dizziness, and gastrointestinal disturbance. Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. **Dosage:** One tablet upon retiring. Where necessary, dosage may be increased to one tablet following the evening meal and one tablet upon retiring. **Supplied:** Bottles of 100 and 500 tablets.

THE NATIONAL DRUG COMPANY
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Quinamm™
(quinine sulfate 260 mg., aminophylline 195 mg.)

Specific therapy for night leg cramps

It's the Law

Seller's Liability

For a Defective Product

A new rule of law has evolved with respect to a seller's potential liability for the sale of a defective product which causes injury or damage. This new rule of law is termed "strict liability in tort," and is best understood in the context of the historical background, in which it was preceded by two general theories of law that dealt with the manufacturer's or seller's liability: negligence and warranty.

Negligence

From the time of the decision of the New York Court of Appeals* involving a defective automobile wheel, the courts have imposed liability against the manufacturer who negligently manufactured or designed a product and sold it in such condition as to render it dangerous. The injured user could recover damages even though he had not purchased the product from the manufacturer. Negligence might consist of failure to adequately test the product prior to sale, or failure to adequately inspect it to determine the presence of any defects. It was necessary, however, for the injured user to affirmatively prove that in some respect the manufacturer was negligent. It was not sufficient for him simply to show that the product was defective and that the defect rendered it dangerous.

Warranty

Warranty has evolved over a period of many years and is primarily a result of the interpretation placed on the Uniform Sales Act by the courts of the various states. The Uniform Sales Act does not specifically deal with recovery of damages for injuries caused by defective products but nevertheless has been the vehicle by which the courts have reached that result. The Act deals with both express and implied warranties. An express warranty is simply an affirmation of fact which tends to induce a consumer to purchase the product. The more important provisions of the Act in the growth of products liability law were those dealing with the so-called implied warranties, and particularly that provision which states that in the absence of any agreement to the contrary, the seller is deemed to warrant that the product is of "merchantable quality." The courts came to hold that a product which was defectively manufactured, so as to render it dangerous, and which, in turn caused injuries and damage, was not of merchantable quality, and therefore the seller had breached the implied warranty of merchantability.

There is no requirement that the injured consumer prove that the manufacturer or seller was in any way negligent. On the other hand, these warranties, whether express or implied, were a matter of contract and, therefore, only the purchaser could claim a breach of warranty, and then only as against the company from whom he purchased. The courts gradually expanded the concept of "purchaser" so as to include members of the immediate family, corporate employees and the like, but were nevertheless limited by the contractual concept of this theory of recovery. In addition, since warranty was a matter of contract, it could be contracted away, and this became the uniform

*McPherson v. Buick Motor Co., 217 N.Y. 382, 111 N.E. 1050 (1916).

practice on the part of manufacturers and commercial sellers. It was done by means of written disclaimers, or by a form of written warranty which provided only for a replacement of defective parts and was to be in lieu of any and all other warranties, express or implied. Thus, within the conceptual framework of warranty it was possible for manufacturers and sellers to avoid any warranty liability.

To summarize very generally, a consumer could recover on proof of negligence in manufacture even though the consumer did not purchase from the manufacturer; or the consumer could assert a breach of warranty against that person from whom he purchased a product, without any proof of negligence, but only if there was no disclaimer of warranty. Proof of negligence by the manufacturer is usually difficult and expensive and, with the widespread use of disclaimer of warranty, the consumer had no effective remedy against the immediate seller and thus as a practical matter was often left with no legal remedy at all.

Strict Liability in Tort

The doctrine of "strict liability in tort" has now been adopted by many state and Federal Courts and, as promulgated by the American Law Institute in Restatement, Torts 2d, S 402A, is as follows:

"S 402A. Special Liability of Seller or Product for Physical Harm to User or Consumer.

"(1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if

(a) the seller is engaged in the business of selling such a product, and

(b) it is expected to and does reach the user or consumer without substantial change in the condition in which it is sold.

"(2) The rule stated in Subsection (1) applies although

(a) the seller has exercised all possible care in the preparation and sale of his product, and

(b) the user or consumer has not bought the product from or entered into any contractual relation with the seller."

This new concept now obviates the necessity of proof of negligence, and also imposes a form of liability quite similar to breach of warranty liability but without the contractual elements which make it possible for a manufacturer to disclaim any responsibility.

It should be realized that a consumer must show that a product was defective in order to assert a claim for damages. The rule of "strict liability in tort" does not mean absolute liability. As to the definition of the term "defective," the Courts are looking to their older decisions in the field of implied warranty of merchantability in order to evolve rules or tests that will distinguish between a defective and a non-defective product. Thus, at least as a general conceptualization, it can be said that the scope of the duty of a manufacturer as to the kind of product he must produce is not greatly changed by the rule of strict liability in tort. Rather, the benefit of this new doctrine to the consumer is that he, while required to prove that the product was defective, is not required to go one step further and prove that the defect arose through negligence.

Robert J. King*
Attorney

*Minneapolis, Minnesota.

Do good to thy friend to keep him, to thy enemy to gain him.—Benjamin Franklin.

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Now that there's a greater therapeutic potential for treating Parkinson's disease and syndrome

...the information on these pages will be of practical interest to you

Larodopa® (levodopa) Roche : therapy that demands slow, individualized dosage titration

With the advent of new Larodopa (levodopa), there is now an agent that holds promise of relief of all the major symptoms of Parkinson's disease and syndrome—rigidity and akinesia as well as tremor.

However, as has been reported in the medical literature, levodopa demands slow, careful titration of dosage, and frequent patient monitoring. Adverse reactions may occur at any time, some serious enough to require dosage reduction or discontinuance of therapy. Thus, before prescribing, it is particularly important to refer to the following Important Therapeutic Considerations, the sections covering dosage and administration, and to the information on monitoring the patient (see prescribing information).

Important Therapeutic Considerations

Larodopa (levodopa) is an unusual drug which must be administered with particular care. In view of its high incidence of adverse reactions, you will find the following therapeutic considerations for Larodopa important:

(a) Larodopa is not curative and its mechanism of action is unknown, though postulated.

(b) Long-term safety and efficacy for Larodopa have not been established.

(c) Accurate diagnosis is imperative since there is no evidence that Larodopa is effective in neurological diseases other than Parkinson's disease and syndrome.

(d) About one-third of patients or more will not experience clinical improvement on Larodopa, and virtually 100% of patients will experience side effects of some degree.

(e) The dose of Larodopa producing maximal improvement with tolerated side effects must be *carefully titrated for the individual patient.*

(f) Finally, there is no evidence that early treatment with Larodopa, while possibly controlling symptomatology, alters the course of the disease.





Photographs of patients treated with Larodopa by permission of the patients.

Guide to dosage and administration of Larodopa® (levodopa)Roche

Usual daily dosage—initially, 0.5 to 1 Gm daily (divide 2 or more doses with food).

Total daily dosage—increased gradually in increments of 0.125 to 0.75 Gm every 2 or 3 days, as tolerated.

Usual daily dose range—from 4 to 6 Gm given orally in 3 or more divided doses, with food.

Daily dosage should NOT exceed 8 Gm.

Optimal therapeutic dosage—usually reached in 6 to 8 weeks.

Establishing optimal dosage—must be determined and *carefully titrated for the individual*—gradually increase dosage until: (1) maximal response is seen, or (2) maxim recommended dosage is reached, or (3) side effects preclude further dosage increase, or require reduction discontinuation of dosage.

Interrupted therapy—after brief interruption, dosage should again be adjusted gradually. (In many cases, the patient can be rapidly titrated to his previous therapeu dosage. See "Precautions" section of Complete Prescrib Information.)

To underscore the extreme importance of careful dosage titration, the following week-by-week dosage pattern has been prepared, based on the assumption that the course o therapy is uninterrupted by any complications requiring a change in dosage. (Again, dosage must be reduced whe intolerable side effects occur.)

Because it is absolutely imperative that Larodopa therap be individualized to meet the particular needs of each patient, the following dosage schedule should be consider only a model.

Larodopa®
levodopa/Roche

tration of Larodopa (levodopa) dosage i patient evaluated weekly

ervals	0.25 Gm Tablets	0.5 Gm Tablets	Total Daily Dose
ek 1	½ tab (0.125 Gm) *q.i.d.* w/ food		0.5 Gm
ek 2	1 tab (0.25 Gm) *q.i.d.* w/ food		1.0 Gm
ek 3	1½ tab (0.375 Gm) *q.i.d.* w/ food		1.5 Gm
ek 4		1 tab (0.5 Gm) *q.i.d.* w/ food	2.0 Gm
ek 5		1½ tab (0.750 Gm) at breakfast and dinner. 1 tab (0.5 Gm) at lunch and bedtime	2.5 Gm
ek 6		1½ tab (0.750 Gm) *q.i.d.* w/ food	3.0 Gm
ek 7		2 tab (1.0 Gm) at breakfast and dinner. 1½ tab (0.750 Gm) at lunch and bedtime	3.5 Gm
k 8		2 tab (1.0 Gm) *q.i.d.* w/ food	4.0 Gm

e daily maintenance dosage in the above example may increased, decreased, or maintained at the 4 Gm level pending upon the point at which optimal therapeutic ults are achieved.

ncurrent therapies: Larodopa (levodopa) may be used ncomitantly with other antiparkinsonism drugs such as ztropine mesylate (Cogentin), trihexyphenidyl HCl rtane) or procyclidine HCl (Kemadrin), but when more n one drug is used, the usual dose of each may have to reduced.

t to be given concomitantly: MAO inhibitors. Such nts must be discontinued two weeks prior to initiating rodopa therapy.

te of caution for patients who require vitamin plementation: It has been reported that pyridoxine HCl tamin B_6) can rapidly reverse the antiparkinson effects evodopa therapy.

timetable for monitoring

ile it cannot be emphasized too strongly that each ient on Larodopa must be treated as a totally *distinct* ity, the following are suggested as guidelines in the nitoring of such patients.

For the first month, at least: the average ambulatory patient should be seen and evaluated a minimum of *once eek.*

During the second month: patient evaluations can be ended to *every two weeks* (assuming no laboratory normalities or intolerable side effects have occurred).

3. From the third through the sixth month: the patient should be evaluated *once a month.*

4. After six months on the appropriate maintenance dose: with no significant adverse reactions or laboratory abnormalities, the patient should be seen at least *once every two months.*

5. Finally, after one year on maintenance dosage: evaluation should be made no less than *once every three months.*

Therapeutic response

A favorable response may often be seen within 10 days to several weeks. However, a patient should not be taken off a tolerable dose—even in the absence of a response—until six months have elapsed. This is because, in some instances, the response may come relatively late. Of course, any serious laboratory abnormalities or intolerable side effects automatically dictate discontinuance of therapy.

Lessening the side-effects problem

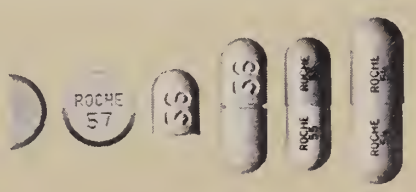
While it is generally advisable that levodopa be taken after meals, nausea and vomiting, two frequently occurring side effects of levodopa, can often be minimized by taking medication with foods. If nausea becomes intolerable, the dosage should be cut back in daily decrements equal to the most recent increments given the patient. This reduction is to be spaced over two- or three-day intervals. Conversely, as nausea subsides, the drug dosage should be slowly increased in like increments.

An important part of the routine monitoring procedure would be to determine any possible cardiovascular problems. If cardiac arrhythmias occur, Larodopa should be discontinued and other antiparkinson therapy instituted.

With orthostatic hypotension a possibility, checking the patient's blood pressure (both supine and standing) is essential.

If choreiform movements appear, they usually occur when maximum therapeutic dosages are reached. To control such effects, reduce dosage by decrements of 0.5 Gm daily.

Flexible dosage: scored tablets of 0.25 Gm and 0.5 Gm help simplify dosage titration



Conveniently scored 0.25 and 0.5 Gm tablets make possible more precise titration. Should another dosage form be preferred, Larodopa is also supplied in capsule strengths of 0.25 and 0.5 Gm.

Before prescribing, please consult product information on next page. →

For the relief of symptoms associated with Parkinson's disease and syndrome

Larodopa®
levodopa/Roche

Before prescribing, please consult complete product information. a summary of which follows:

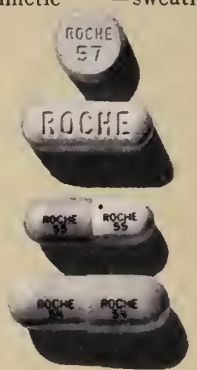
BECAUSE OF THE HIGH INCIDENCE OF ADVERSE REACTIONS AND THE NECESSITY FOR INDIVIDUALIZING THERAPY, THE PHYSICIAN SHOULD THOROUGHLY FAMILIARIZE HIMSELF WITH THE INFORMATION IN THE PACKAGE INSERT BEFORE INSTITUTING THERAPY WITH LARODOPA (LEVODOPA). ACCURATE DIAGNOSIS IS IMPERATIVE BECAUSE EVIDENCE IS LACKING THAT LARODOPA IS EFFECTIVE IN NEUROLOGICAL DISEASES OTHER THAN PARKINSON'S DISEASE AND SYNDROME.

ADEQUATE CLINICAL AND LABORATORY FACILITIES SHOULD BE AVAILABLE FOR PROPER MONITORING OF TREATMENT.

THE LONG-TERM SAFETY AND EFFICACY OF LARODOPA HAVE NOT BEEN ESTABLISHED.

Indications: For the treatment of Parkinson's disease and syndrome. Useful in relieving many of the symptoms, particularly rigidity and bradykinesia; frequently helpful in management of associated tremor, dysphagia, sialorrhea and postural instability.

Contraindications: In patients for whom a sympathomimetic amine is contraindicated; in patients receiving MAO inhibitors (the latter should be discontinued two weeks prior to initiating therapy with Larodopa); in patients with clinical or laboratory evidence of **uncompensated** endocrine, renal, hepatic, cardiovascular or pulmonary disease; with narrow angle glaucoma and blood dyscrasias; in patients with known hypersensitivity to levodopa.



Warnings: Long-term safety and efficacy not established. Administer with extreme caution to patients with bronchial asthma or emphysema who may require sympathomimetic drugs; to those with active peptic ulcer (in facilities equipped to treat gastrointestinal hemorrhage); in patients with psychoses or severe psychoneuroses. Initiate therapy with extreme caution and in proper treatment facility in patients with a history of myocardial infarction who have residual atrial, nodal or ventricular arrhythmias. Monitor all patients for development of mental changes, depression with suicidal tendencies, other serious antisocial behavior. Carefully consider concomitant administration of pyridoxine hydrochloride (vitamin B_6); oral doses of 10 to 25 mg have been reported to rapidly reverse the antiparkinson effects of Larodopa. In pregnancy, weigh potential benefits against possible hazards. Do not use in nursing mothers. Safety of Larodopa in children under age 12 not established.

Precautions: During extended therapy, periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function recommended. In diabetic patients, control may be adversely affected; careful, frequent monitoring and proper adjustment of antidiabetic regimen required. Patients with chronic wide angle glaucoma may be treated cautiously provided intraocular pressure is well controlled and patient is monitored carefully. Monitor carefully patients receiving antihypertensive agents or psychoactive drugs concomitantly, or those with history of convulsions. If general anesthesia is required, discontinue Larodopa 24 hours prior to surgery; monitor cardiorespiratory functions carefully. Patients who improve on Larodopa therapy should resume normal activities cautiously. May be used concomitantly with other antiparkinson drugs with possible reduction in dosage of each.

Adverse Reactions: *Most frequently occurring:* nausea, anorexia, emesis, cardiac irregularities, orthostatic hypotension; choreiform, dystonic and other adventitious movements; dizziness, sedation, dyskinesia; psychiatric symptoms such as agitation, anxiety, confusion, depression, hallucinations, delusions, insomnia, nightmares, and mental changes including paranoid ideation and psychotic episodes. *Less frequently occurring* and listed according to system: *psychiatric*—suicidal tendencies, increased libido with serious antisocial behavior, euphoria, lethargy, stimulation, fatigue and malaise, dementia; *neurological*—ataxia, convulsions, faintness, impairment of gait, headache, increased hand tremor, akinetic episodes, torticollis, trismus, oculogyric crisis, weakness, numbness, bruxism; *gastrointestinal*—constipation, diarrhea, epigastric and abdominal distress and pain, flatulence, eructation, hiccups, sialorrhea, difficulty in swallowing, bitter taste, dry mouth, tightness of mouth, lips or tongue, duodenal ulcer, gastrointestinal bleeding, burning sensation of the tongue; *cardiovascular*—nonspecific ECG changes, palpitations, hypertension, flushing, phlebitis; *hematological*—hemolytic anemia (1 case); *dermatological*—sweating, edema, hair loss, pallor, rash, bad odor; *musculoskeletal*—low back pain, muscle spasm and twitching, blepharospasm, musculoskeletal pain; *respiratory*—feeling of pressure in the chest, cough, hoarseness, bizarre breathing pattern, postnasal drip; *urogenital*—urinary frequency, retention, incontinence, hematuria, nocturia, and one report of interstitial nephritis; *special senses*—blurred vision, diplopia, dilated pupils, activation of latent Horner's syndrome; *other*—fever, hot flashes, weight gain or weight loss.

Nausea, anorexia and vomiting usually obviated by temporary dosage reduction and/or administration with food. If cardiac arrhythmias occur, discontinue and institute other antiparkinson therapy. Reduce dosage when involuntary movements occur.

The following have been noted: elevation of BUN, SGOT, SGPT, LDH, bilirubin, alkaline phosphatase or PBI; occasionally, reductions in WBC, hemoglobin and hematocrit; elevations of uric acid with use of colorimetric method but not with uricase; rarely, positive Coombs test; dark sweat and urine.

Dosage and Administration: Because of the strong possibility of adverse reactions and the necessity for individualizing therapy, the physician should thoroughly familiarize himself with the information in the package insert before instituting therapy.

How Supplied: *Tablets*, pink, scored, containing 0.25 Gm levodopa (imprinted Roche 57) or 0.5 Gm levodopa (imprinted Roche 56)—bottles of 100 and 500.

Capsules, containing 0.25 Gm levodopa (pink and beige, imprinted Roche 55) or 0.5 Gm levodopa (pink, imprinted Roche 54)—bottles of 100 and 500.

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Cover Photo

Baldy at Sun Valley

In the foreground is the Opera House at Sun Valley, Idaho, where the annual meetings of the Northwestern Medical Association have been held since 1947. Baldy Mountain rises in the background, which contains some of the most challenging ski runs in North America.

Photographer: Richard C. Tucker, M.D. of Minneapolis.

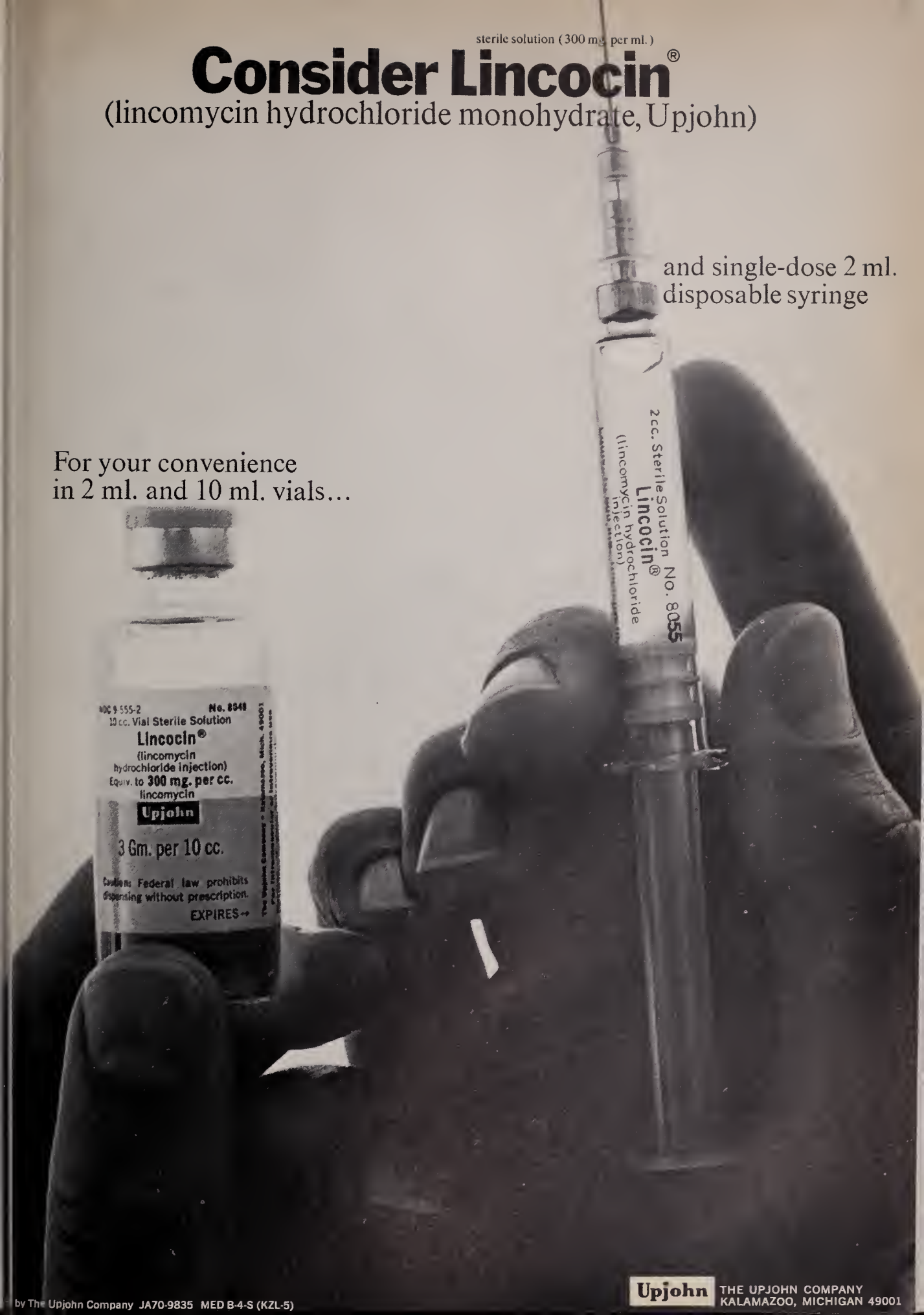
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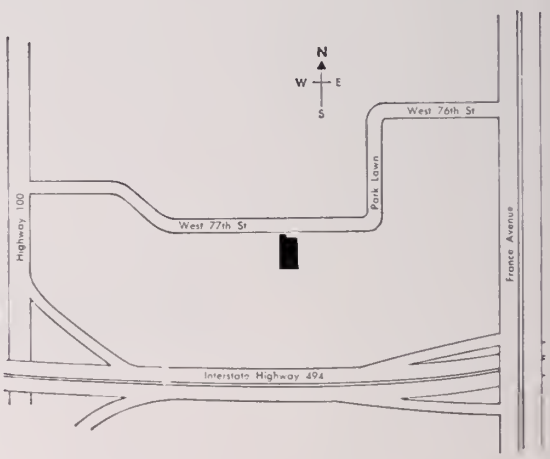
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History

Skiing Down Through the Years

"The new men come out of the wilderness"—Nansen

RICHARD C. TUCKER, M.D.

SKIING AS WE KNOW it is relatively new; however, its evolution bears a direct relationship to its present status. It is apparent that equipment has had a direct bearing on technique, and technique, in turn, has demanded new equipment. What began as a utilitarian means of transportation finally evolved into a sport; thus modern skiing was born.

Archaeology of the Ski

Five thousand years ago in the glacial areas from Norway to the Bering Sea, snowshoes, sleds, skis and skates helped man travel over snow and ice. The word ski, derived from a Germanic-Latin word implying a splitting of wood, is a Norwegian name for snowshoe. According to some observers, the snowshoe preceded the ski; however, Wiklund believed that the ski developed independently of the snowshoe which derived from a furred walking boot. Skis were worn to keep one from sinking too deep into the snow and were not used for gliding. Later, as man become more mobile, they were used in hunting, migration and warfare.

*The decaying process is related to the type of wood. Pine resists decay better than hardwoods; thus, few hardwood skis have been found.

"The origin of the ski is one of those ethnographic phenomena whose development is lost in the prehistoric ages when the mainstream of culture arose."[20] Crude rock engravings in Russia and Norway date back to the 3rd Century B.C.

The earliest known ski, the Hoting Ski,[20] was dug up in a peat bog by Swedish archaeologists in 1921 (Figure 1). Radioactive carbon studies date this ski as a little over 4500 years old; the Ovrebo Ski as 2500 years old, and the Arvtrask Ski as 1500 years old.

The Hoting Ski, made of pine, was five feet long and five inches wide, the under side covered by the pelt of an animal, thus reducing snow clogging and preventing backward slipping: a forerunner of our modern climbing skis. The early skis were made of hard wood and later of fir; however, most of the excavated skis are of pine.*

Prehistoric Skis

Prehistoric skis are divided into three main types, some of which are still extant.

Northern Arctic Type

The Northern Arctic and Southern skis ori-

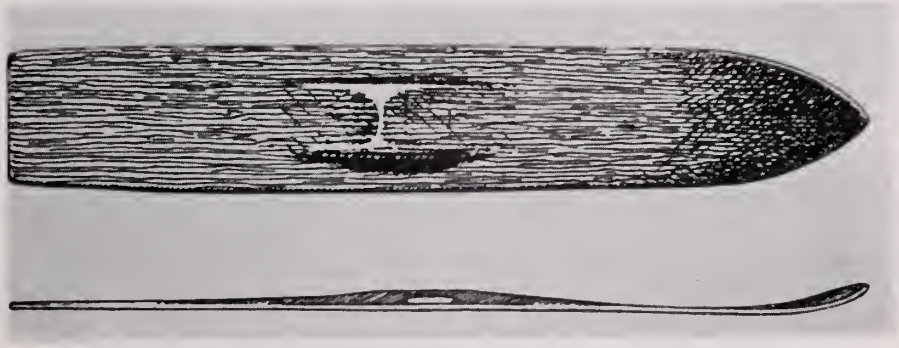


Fig. 1—The Hoting Ski—the oldest ski found in a peat bog in Sweden. It is over 4,500 years old.

ginated independently. No one knows which is the older. The Arctic type was of a good design and has remained basically unchanged throughout the centuries. It was short and wide (5-6 feet long and 6 inches wide); the straps were attached through vertical holes at the top of the ski; the bottom was covered by a hide. This type is still used in Siberia today.

Southern Type

The Southern type ski from Southeastern Europe found its way into Scandinavia where it was altered—from the depressed foot rest into a raised foot rest with a horizontal strap, and finally to the ridgetop ski of the early 20th Century. It was long and turned up at the end, resembling the skis of the 1930s. It had a high sidepiece for toe straps and holes for heel bindings. This ski was used in mid-Europe from the Ural Mountains to Southern Norway.

Central Nordic Type

The Central Nordic type skis were of unequal length. The *left* ski was long and grooved; the *right* ski was short and covered with fur for traction and was called the Andor (Figure 3). These skis were used in Lapland. The groove[20] in the ski, unknown outside of Scandinavia, was introduced by the Norwegians around 500 A.D. The Lapps, Finns, and then the Russians, in turn, borrowed the groove from the Norwegians before the rise of skiing as a sport in the early 1800s.

Recorded History

The Gliding Finns

The first written record regarding skiing was by a historian named Procopius (525-559 A.D.),[29] who mentioned the gliding Finns: Skridfiner, a term used by the German tribes to describe non-Germanic people of the North—Lapps, Finns and Scandinavians—who raced against the non-gliding Finns.

Horse-Footed Men

Ancient Chinese geographers mentioned horse-footed men in the realm of the Ting-ling Dynasty. Other Chinese works, 600-900 A.D., tell of Mongol-Turkish tribes using the "wooden horses, which are described as boards turned up at the front, on which a hunter, with the aid of sticks, can overtake a horse in the snow."[22] Thus we see that man, throughout all the snowy climes of the world, made independent attempts at developing devices to enable him to cross over the snow.

The Vikings

The Sagas of the Vikings relate many episodes of skiing. In 1060 A.D. a race is recorded between Norway's King Harold and Hemings Aslakson, the skier.[9] After 1200 A.D. in Norwegian history (Figure 2), there are many references to skiing, but there is a paucity of any graphic information about it in any other area. It was not until the invention of the printing press in the 16th Century that knowledge of skiing become more widely disseminated.



Fig. 2—"Birch-leg" soldiers carrying the Norwegian king to safety, circa 1200.

The most famous of the early ski books is one by a Swedish Bishop, Olaus Magnus[7,28,29] (1555), who had been exiled to Norway and later wrote about his experiences there. This book is important as it contains many interesting wood cuts, which give us the artists' impressions of the skiers of the time.

In 1673 a German named Johan Scheffer



Fig. 3—Lapp skier published in a Latin work opera Laponia in 1673 by Johan Scheffer.

published a book containing excellent illustrations of skiers using one long and one short ski[29] (Figure 3) (Central Nordic type of ski).

In 1733 the first handbook for Norwegian ski troops was written by Jens Emahusen. As tourists visited Norway, Sweden, and Lapland during the 19th Century, many written reports of men on skis began to filter into other countries. By the mid-19th Century, the immigrating Norwegians were introducing skiing around the world; the first mention of skis in North America was at an Ice Carnival in Canada in 1759.

The Origin of a Sport

Shortly after 1800 we begin to find reports of skiing as a sport enjoyed for its own sake. By that time jumping and ski racing were firmly established in Norway. Elsewhere throughout the world skiing was beginning to be engaged in for both fun and profit. As many of these Norwegian immigrants became miners, skiing found its way all over the globe, to the farthest corners of the earth, even to the Orient (Figure 4).

Sonder Nordheim

In 1825, in the Norwegian province of Morgedahl in the Valley of Telemark, a boy was born who was to become the founder of skiing as a sport. His name was Sonder Nordheim.[16] In 1840 he introduced ski jumping at the end of a gradient and was credited with developing the Telemark turn. Sir Arnold Lunn[16] says of Nordheim: "He discovered the possibility of landing from a jump, not on the flat, as heretofore, but on a steep slope, and thus may be



Fig. 4—California miners speeding downhill with the brakes on in the 1880s. The Norwegian immigrant provided impetus that started skiing in America.

credited with the invention of modern ski jumping. He would finish his jump by coming gracefully to a stop, after extending one leg markedly advanced over the other and steering his ski into a turn," thus inaugurating the Telemark turn. In order to accomplish this, Sonder had to invent a method of holding the heel in place, and this he did by using thin willow roots,* soaking them in hot water so that they would be flexible and then twisting them together to fit around the heel. They were called the osier bindings (Figure 5). At the age of 35, Sonder jumped over 60 feet.

He is also credited with the first new approach to making skis very similar to our present-day models, incorporating a wide shovel and tail with a narrowed waist, which enables the ski to have some turning capabilities of its own. This was called the Telemark ski. It was soft, measuring seven to eight feet, and was of a ridge-top variety to give it more stability and to reduce its weight. Bindings were adequate for the type of skiing done, mainly walking and

*Osier[29]—meaning root.



Fig. 5—The osier binding of 1870, developed by Sonder Nordheim in 1850.

climbing. Heel lift was essential in these early bindings, and that, plus the soft ski tip for the Telemark turns, was ideal. The Nordheim binding and ski, coupled with the competitive spirit of the Norwegians, initiated skiing as a popular sport. Thus, from the obscure village in Telemark, in the province of Morgedahl, the Diaspora habits of the Norwegian immigrant established skiing as a sport around the world.

> "We must keep in mind that discoveries are usually not made by one man alone, but that many brains and many hands are needed before discovery is made for which one man receives the credit."
>
> H. E. Sigerist, 1891-1957

In 1884 Sonder and his family migrated to America and finally settled in North Dakota, where he spent the rest of his life unnoticed. He died, a farmer, on the Dakota prairie in 1892 and was interred in the local cemetery in Denbigh, North Dakota. He continued to remain in obscurity until 1966 when Norwegian friends finally found his burial place and bestowed upon him recognition of his accomplishments by having a memorial plaque placed on his grave by ski dignitaries from around the world. It seems paradoxical that a man who is now acknowledged as the progenitor of modern-day skiing, and who was born and raised and spent two thirds of his life on the mountains, should die in obscurity on the flat, windswept plains of North Dakota, where a ski hill is as rare as a flat farm in Norway.

Snowshoe Thompson

In the 1890s the famous Snowshoe Thompson started to provide the only winter communications between the East and California.[3] His feat added no impetus to skiing but provided a unique anecdote in ski history. He carried the mail over the route of Kit Carson and John Fremont, from Placerville to Carson Valley, 90 miles on skis. This was arduous work, but Thompson persevered in this endeavor for over 20 years. It took the Pony Express and the railroad to replace him. His skis were crude: made by himself of oak, weighing about 20 pounds each, measuring about 12 feet in length, and having a single leather thong to hold the toe in place with a small block of wood behind the heel. Usually it took him about 16 ski hours to make the trip. Ironically he received little official recognition and very little pay for his efforts, but his memory is perpetuated by the legend of Snowshoe Thompson.

Mikkel Hemmestviet

Through the influence of the Norwegian immigrants, ski jumping became popular in Colorado, Wisconsin, Minnesota, Montana and the New England states. In 1891 at Red Wing, Minnesota, Mikkel Hemmestviet set the world jumping record of 102 feet. Both he and his brother had been taught by Nordheim. Skiing was mainly jumping, cross country navigation, or straight downhill running, with very little turning except for the Telemark. This limitation was primarily due to the fact that the bindings and boots had not been developed sufficiently to enable one to control his skis. The ski techniques had been adapted to the open, rolling hills of Telemark and Christiania, Norway.

Introduction of Skiing to Central Europe

From 1875 to 1900 archives and books refer to many individuals who pioneered skiing as a sport in the Central Alpine areas of Europe.

Sir Arnold Lunn

While many Austrians, Germans and Swiss worked intently to develop a new Alpine technique, much of the credit must go to British sportsmen,[6,7,15,16,24,29] in particular Sir Arnold Lunn.

He spent a great deal of time skiing in Switzerland and made detailed studies of ski techniques, equipment, and snow conditions, and has written many books on the subject, of which his most famous is the *History of Skiing*,[15] published in 1927. He has the unique distinction of originating the Downhill and Slalom races as we know them today. He is the only man alive who has actually invented a sport adapted to the Olympic Games.

Many Englishmen in the 1880s and 1890s who learned to ski while vacationing in Norway brought skis to their summer playground in Switzerland, and it was the British who encouraged the Swiss inkeepers to keep their hotels open in the wintertime so that vacationers could practice skiing. Sir Arthur Conan Doyle made the first crossing on skis from Davos[16] to Arosa in 1894, and E. C. Richard-

son and Vivian Caulfield were important early British ski pioneers. Caulfield's book,[6] *How to Ski,* became a classic on ski instruction; he recommended dispensing with the single stick and lucidly described a Christiania turn, which had not been previously done.

Fridtjof Nansen

There is no doubt that one of the most important factors influencing skiing in Central Europe was the book by Fridtjof Nansen,[15,19,28,29] titled *Paa Ski Over Gronland,* published in 1890, wherein the author described a 40-day journey on skis with three other Norwegians and two Lapps. Dragging their equipment on sledges across Greenland from East to West, they traveled over 300 miles. They used oakwood skis with three grooves, without toe irons, but with a binding that Nansen had devised (Figure 6). He used a long stick for part of the journey, but he preferred two six-foot sticks on hard snow and ice. Nansen's book, translated into many languages, was exceedingly popular. The following is a passage therefrom:

> "Of all the sports of Norway, skiing is the most national and characteristic; as practiced in our country it ranks first in sports of the world. Nothing hardens and makes the body so strong and elastic; nothing gives a better presence of mind and nimbleness; nothing steels the will power and freshens the mind as skiing. This is something that develops not only the body, but also the soul—it has far deeper meaning for people than many are aware of and a far greater importance than is generally supposed."

Nansen was the first to describe why skis glide over snow. He found that the friction between the wood and the snow crystals produced heat which in turn produced a thin layer of water.[19] When sub-zero temperatures (−20 to −30 degrees) are encountered, hickory, a fair heat conductor at this temperature, adheres to the snow surface because the heat of friction enters the ski and causes the snow to stick to it. On the other hand, birch is a poor heat conductor at low temperature; consequently this ski functions well in cold weather.

Wilhelm Pauleke (German), Colonel Iselin (Swiss), and Mathias Zdarsky (Austrian), three of the early pioneers, were profoundly influenced by Nansen. Pauleke was given skis as a Christmas present from his Norwegian tutor and later became one of the first pioneers of ski mountaineering in the Alps. It was he who probably began linking Telemark turns down a slope, thus introducing the first linked S turns.

Dr. Henry Hoek, in 1906, wrote a book called *Der Ski,* which was based on Norwegian technique and the stem technique of Zdarsky. Colonel Christopher Iselin is regarded as the father of Swiss skiing.

Mathias Zdarsky

Of all the early pioneers, Mathias Zdarsky[15,17,27] (1874-1946) is regarded as the father of Alpine ski technique. It was the German translation of Nansen's book[19] that transformed Zdarsky into a skier. A man of private means who had been a youthful athlete of renown, Zdarsky was an excellent gymnast and also a mountain climber of distinction. In 1889 he retired to his mountain home of Hbernreith, where he lived like a hermit and began to put into practice what he had read from Nansen's book regarding ski techniques. He skied alone and continually experimented with downhill skiing. His main aim was to make skiing safe for touring the high country and then to descend the mountain safely and under control. This was an entirely new approach, as the Norwegians did not have steep slopes to contend with. In order to do this he soon found that the steep slopes were a challenge and it was necessary to develop a system of close-linked



Fig. 6—The ski used in Nansen's expedition. This is a forerunner of the Telemark ski. The boot and binding were used by Nansen. The binding was called "Lauparsco" from "The First Crossing of Greenland."

turns. Zdarsky called these S turns and he invented, or so he thought, the snowplow and the stem turn. He maintained control by relying on a long wooden stick without a disc. "The stick was not to be used as a means of support, but rather as an instrument to feel or grope with." He advocated trailing the stick to produce a steady position. Occasionally the pole was used as a pivot. Living alone and experimenting as he did, Zdarsky merely rediscovered what others had done in Norway and Germany: information no one had yet put into writing.

Lilienfeld, a Province in Austria

From his intense study of Norwegian skiing techniques and his own inventive application, Zdarsky developed skis and bindings which bore the name of his Austrian homeland—Lilienfeld ski and binding. His skis were short and grooveless, about five feet long and four inches wide, with bindings that were a definite improvement over the birchwood osier binding of the Norwegians. His skis turned easily but were not made for fast skiing.

His mechanical metal binding was adjustable to various boot sizes and permitted no lateral movement, thereby enabling the ski to be steered with accuracy. The pivot point of this binding was in front of the boot, thus preventing the forward lean and causing a tendency to rucklage (backward lean)—no doubt delaying the development of vorlage (forward lean). The boots of that day were much like our modern work-day shoes and provided little stability.

In 1896 Zdarsky wrote the first methodical analysis of skiing technique called the *Lilienfelder Ski Lauf Technik*. By 1908 he had started a ski school which soon had over 1200 pupils. This was the first successful attempt to develop a didactic type of ski school. Zdarsky deservedly retains the distinction of the father of Central Alpine skiing. He laid the foundations upon which other Germans, Austrians and Swiss, notably Hannes Schneider, Colonel Bilgeri and others could build.

Skiing as of the Early 1900s

Bindings

Until Zdarsky devised his Lilienfeld binding the ski was basically the type that Nordheim had developed in the mid-1800s. A Norwegian by the name of Huitfeld[20] contrived a binding in 1905 that was a considerable advance over Zdarsky's.[9] This consisted of an upward bent piece of metal mortice attached to the ski where the toe of the boot engaged on each side. Leather straps were then attached diagonally from this to hold the heel in place. This binding, with minor improvements, mainly the Ellefsen clamp and later the Bildstein spring, was used up to the 1930s when it became known as the beartrap. The Bildstein spring could be considered a forerunner of our modern release binding, as this spring would usually release during a twisting fall. Further demands for improved ski technique required better bindings which, in turn, yielded better control—an upward spiraling of improving technique and equipment which has continued to this day.

Beginning of Modern Downhill Skiing

A masterly-written book called *Der Alpine Skilauf*[21,28,29] by Colonel G. Bilgeri presented a combination of the best of the Norwegian and Zdarsky techniques: a deep crouch, stemming the ski at right angles to descent, use of a short ski (five feet), a skating stride, and the first introduction of two shorter ski poles. In this book, Bilgeri introduced the stem christie and maintained that skis should be edged or flat, depending on the need. There is no doubt that the Arlberg system, as evolved later under Hannes Schneider, derived a great deal of its basic mechanics from Bilgeri.

The Birth of the Arlberg Technique

The Deep Crouch

In 1907 Hannes Schneider[25,28,29] began teaching a technique that he had developed through trial and error in the village of Stuben am Arlberg. He discarded the cautious one-pole technique of Zdarsky's Lilienfeld technique and used two poles, introducing the *snowplow*, the *stem christie*, and the *deep crouch*. This, together with Schneider's personality and genius of organization, made the Hannes Schneider Ski School the prototype of modern day ski schools. He had found that the popular Norwegian Telemark turn was inadequate, as it was too slow and could not be adapted to the steep terrain of the Alpine mountains. During World War I he was given a responsible position training the Austrian Alpine troops, there-

by providing him with valuable experience in developing his skiing ideas.

The Ski Boots

By this time ski boots were being made, comprised of thick, square soles which would not buckle from the mild diagonal tension of the Huitfeld binding. The idea for the need of lateral support did not arrive until about 20 years later. Some of Hannes Schneider's famous teaching staff to migrate to the United States were Otto Lang, Lueggi Foeger, and Benno Rybizka.

Forward Lean and Stemming

In 1921 Hannes Schneider was featured by Dr. Fanck in two full-length ski films—*A Fox Chase in the Engadine an das Wunder des Schneeschus.* These pictures became world famous as they demonstrated to the masses that skiing could be really different from what they were accustomed to seeing and that fast downhill skiing, under control, and in all kinds of snow was possible. Later the two men collaborated on a book called *The Wonders of Skiing.*[25] This was truly a unique book, as it graphically portrayed the Hannes Schneider skiing technique, showed the importance of vorlage (leaning forward) when initiating a christie and demonstrated that his parallel turn was initiated by stemming, though ever so slightly.

The Heel Bindings

Once again, equipment kept pace with advancing technique. In 1928 Thorlauf Haug[20] added two pivot points to the metal toe piece, thus providing for a heel portion of the binding to be hooked into the pivot leads at the side of the plates, leading directly to the traction type of binding.

Racing demanded a more rigid connection between the boot and the ski, and in 1930 a Swiss named Amstutz[20] invented a spring device to hold the heel down. Numerous modifications during the next few years produced Reuge's all-metal cable binding: the Kandahar-Alpha-Attenhofer's cable which provided for a precise adjustment, and finally the first release binding by H. Hvam in the late 1930s.

In 1910 Rickmers,[24] an early English ski writer, penned the following:

"To all ski runners!
The ski binds us, but the binding divides us!
Let us not look downward at a man's feet to see how they are bound;
But let us rather look into his eye, his head and his heart,
That we may know his will and manliness.
So be it!
Ski Heil."

One wonders what Rickmers would think if he were living today, with the present controversy regarding the various bindings and the number of bindings available (150-200).

The Modern Technique

Vorlage has now come of age, skiers crouch less and bring their feet close together.

The Steel Edge

In 1930 an Austrian engineer named Rudolph Lettner, Salzberg,[14,20] invented the steel edge. This was very controversial at first but finally gained wide acceptance, as it provided for more precise control of the ski and initiated the evolution of modern ski technique. His main aim was to increase the longevity of the ski edge, rather than provide for better control; but, serendipitously, this was another instance where the improved equipment provided the opportunity for an advance in technique. Up to this time the Arlberg technique had been the gospel of the ski world.

Reverse Shoulder

In 1934 Dr. Kurt Reine and Toni Ducia in Austria and two Swiss named G. Testa and Professor E. Matthias independently wrote books describing the twisting concept (reverse shoulder technique).[29] Their ideas were too advanced for their time and no one paid any attention to them. This, however, was soon to change.

The Parallel Technique

In the early 1930s, Tony Seelos, a young Austrian ski professional won practically all of the races[7,27,29]; but, as he was a professional, he did not enter the Olympics. The secret of his winning was due to his superb technique in using the parallel turn, an upright stance, and the sequence of rotation, counter rotation and angulation. First, he was a superb athlete, and second, skiing equipment (steel edges, firm skis and rigid bindings) provide a skier with the necessary control. It should be noted, however, that boots at this stage were still deficient in

lateral support, although they were firmer than earlier models. However, it was probably only because Seelos was such a superb athlete with strong ankles that he was able to ski as well as he did.

The French Technique

Emile Allais

In 1936 Seelos became coach of the French ski team. Emile Allais, a young racer on the team, took particular note of Seelos' way of skiing.[28,29] He quickly adapted it to his style, improved and amplified on Seelos' technique, and came up with the so-called French method of skiing, or parallel technique.[1] To do this he improved first on the lateral support of the ski boot by using long thongs. He moved the mortice back from under the toe to just under the anterior part of the heel and bound the boot down with seven to eight feet of leather thong, thus providing an excellent direct lateral control over the edging of the ski while allowing forward lean. The Allais stressed the side slip, counter rotation, marked vorlage and a pronounced up-and-down motion.[1] Allais' famous *ruade* became his trademark, and during the next few years he became the skier to beat. In 1936 he wrote a book called *Ski Francais*[1,29] which described his approach to skiing. This was translated into English in 1947 and is one of the most beautifully illustrated ski books ever published.

Up-Hill Transportation

During the 1940s and 1950s an intense interest in skiing developed throughout the world, primarily due to development of up-hill transportation such as the funiculars, and the cable cars in the Alps. The first "T" bars appeared in Switzerland in 1935 and the first chair lift in the world was built at Sun Valley in 1936. The first rope tow in the United States was at Woodstock, Vermont, in 1934. The *piste* (packed slope) also came of age. This enabled the beginning skier to ski down a slope without being an expert.

Austrian Influence

Following World War II, there was a tremendous resurgence in skiing interest; the French method began to decline in the early 1950s and there was a brief resurgence of the Arlberg technique, which was popularized by such Austrian skiers as Frans Gabl, Eddie Mall, Hans Nogler and Christian Pravda, who merely updated the old Arlberg method by using a more upright and parallel version of Schneider's original technique. Releasable bindings began to proliferate; boots became firmer, and ski poles became lighter and easier to handle; ridgetop skis disappeared and softer flattop skis came into vogue.

The Short Swing

In the early 1950s the Austrians began winning again. Their racers were using a new technique: a rapid waggling motion called the wedeln.[10,21] Under the direction of Stefen Kruckenhauser this technique was analyzed thoroughly and, in 1955, he published the official Austrian Ski Teaching System.[21] Basically, this consisted of thrusting the heels in one direction while the shoulders turn in the opposite direction as a counter force, as had been previously described by Reine, Ducia, Testa and Matthias in 1934. This reverse shoulder movement was a true revolution in skiing. In addition, Reine et al. had instituted a rather marked angling into the hill with the body in a comma position. In order to utilize this as a ski teaching method Kruckenhauser combined the best of the Austrian and French methods to come up with the so-called short swing approach (wedeln).

The Split Rotation, Serpentine Turn and Avalement

With the return of the French to supremacy in racing in the 1960s their skiing techniques again began to approach a more natural stance, less angulation and shoulder reversing, and the so-called split rotation. They even returned partially to the old counter rotation method, with a rather strong heel thrust. With the success of the French in the last Olympics, as personified by Killy, the French technique continues in vogue with the so-called serpentine turn[12] and the avalement approach. This constitutes a rather marked departure from the true parallel stance whereby the French now advocate having the skis several inches apart, with a return to a slight rucklage or sitting back on the tails of the skis (avalement).

The Evolutionary Circle

We have now completed the circle of ski

technique, returning basically to the original Arlberg technique with some modifications. What was supposedly new is not new at all but merely a re-emphasis of some skiing motions now possible because of improved equipment.

By the mid-1940s all of the major concepts of modern Alpine skiing, equipment and techniques had been discovered; only some details remained to be improved upon. The difference between the Austrian, French and so-called American technique is just a matter of degree and doing what comes naturally.

With the advent of the metal ski by Howard Head in 1950 and further refinements, combining metal-fiberglass or fiberglass alone, skis have become much better, reacting more quickly to the skier's motions. We are reverting to a softer ski similar to the type used in the early 20s and 30s, which improve technique remarkably. In addition, further refinements in equipment are directed mainly at greater support of the foot, with more comfort and convenience. The modern ski is a marvel of engineering, and undoubtedly further improvements will occur; but basically the ski has not changed in its overall conformity from that of the last 20 to 30-year period. Once again we revert to the age-old chicken and egg problem. Do the needs of modern technique give rise to the development of the modern ski equipment or does new equipment lead to better and new techniques? Obviously one depends on the other.

Skiing techniques and equipment are constantly evolving and nothing is ultimate or categorical. One can well ponder what the future holds. Perhaps we have placed too much evidence on racing. The majority of skiers are not racers but are just out for fun. The ultra-stiff boots and skis are not for the recreational skier. Otto Schneibs has stated that "skiing is a way of life;" but perhaps a more reasonable approach to skiing is that of Sir Arnold Lunn,[16] who has said that "skiing is a great sport to be enjoyed and not a substitute for religion, and its main purpose is to increase the sum total of fun."

Skiing is freedom, freedom to use your skis as you want; not merely to master the mountain, but to become part of it. To ski well is elegance and grace in motion: the chief aim being to ski down a mountain in control, with ease and safety.

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Greetings

The present issue of Minnesota Medicine is devoted for the most part to diseases of the liver. Pursuing their efforts to apprise their readers of medical developments in foreign countries,the Editorial Board has secured contributions from Parisian clinicians and clinical investigators.

This worthwhile initiative comes at a time when a French journal of clinical investigation is publishing articles in English. Thus, to present a series of articles by French contributors in an American Journal constitutes a commendable further attempt to bridge a communications gap not necessarily related only to language difficulties.

In selecting the school of hepatologists led by my friend René Fauvert of the Hôpital Beaujon, the Board has demonstrated particular knowledge and insight in regard to the arcana of French medicine. René Fauvert has for the past 30 years established his preeminence as a medical scientist, educator, and reformer. He was a member of a small group of physicians who adopted the full-time system in the newly erected Beaujon. With a few colleagues in other hospitals under the leadership of Dr. Robert Debré, he was instrumental in drawing plans for reform of the hospital-university system in France. The program of health-care delivery and medical education has weathered many crises during the past 20 years. The plan finally adopted is presented by Fauvert in this issue.

In addition to paying tribute to a friend, I have other reasons for being pleased to write this foreword. My entire education, humanistic and medical, was obtained in the Parisian university and hospital system. With this background, my integration into American medicine was bound to be rewarding. Furthermore, during my frequent visits to my native city, I often had opportunity to appreciate the organization and to enjoy the invigorating atmosphere of the closely knit group of investigators at Hôpital Beaujon, which reminded me of the best that can be found in this country.

Finally, it has been one of my strong motivations to assist in the development of close relations between French and American physicians. It is my hope that the present issue will not only add to common understanding, in this instance based on the appreciation of valuable scientific contributions, but also herald the coming of a similar opportunity in other medical fields.

André Cournand, M.D.*
New York, New York

*College of Physicians & Surgeons of Columbia University, Department of Medicine.

Nobel Prize

André Frédéric Cournand, M.D., in 1956, shared the Nobel prize in Medicine (with D. W. Richards, M.D. and Werner Forssmann, M.D.) for their basic research in cardiocirculatory and pulmonary functions and the development of the clinical technique of cardiac catheterization.

The original work on heart catheterization was done in 1929 by Dr. Forssmann in experiments on himself. At that time Dr. Forssmann's colleagues regarded him as a crackpot and his friends persuaded him to drop the researches.

It was further interesting to note that Dr. Cournand and Dr. Richard, discovering Dr. Forssmann's paper, realized its merit and proceeded to conduct their own experiments, first on animals and then on humans.



President's Letter

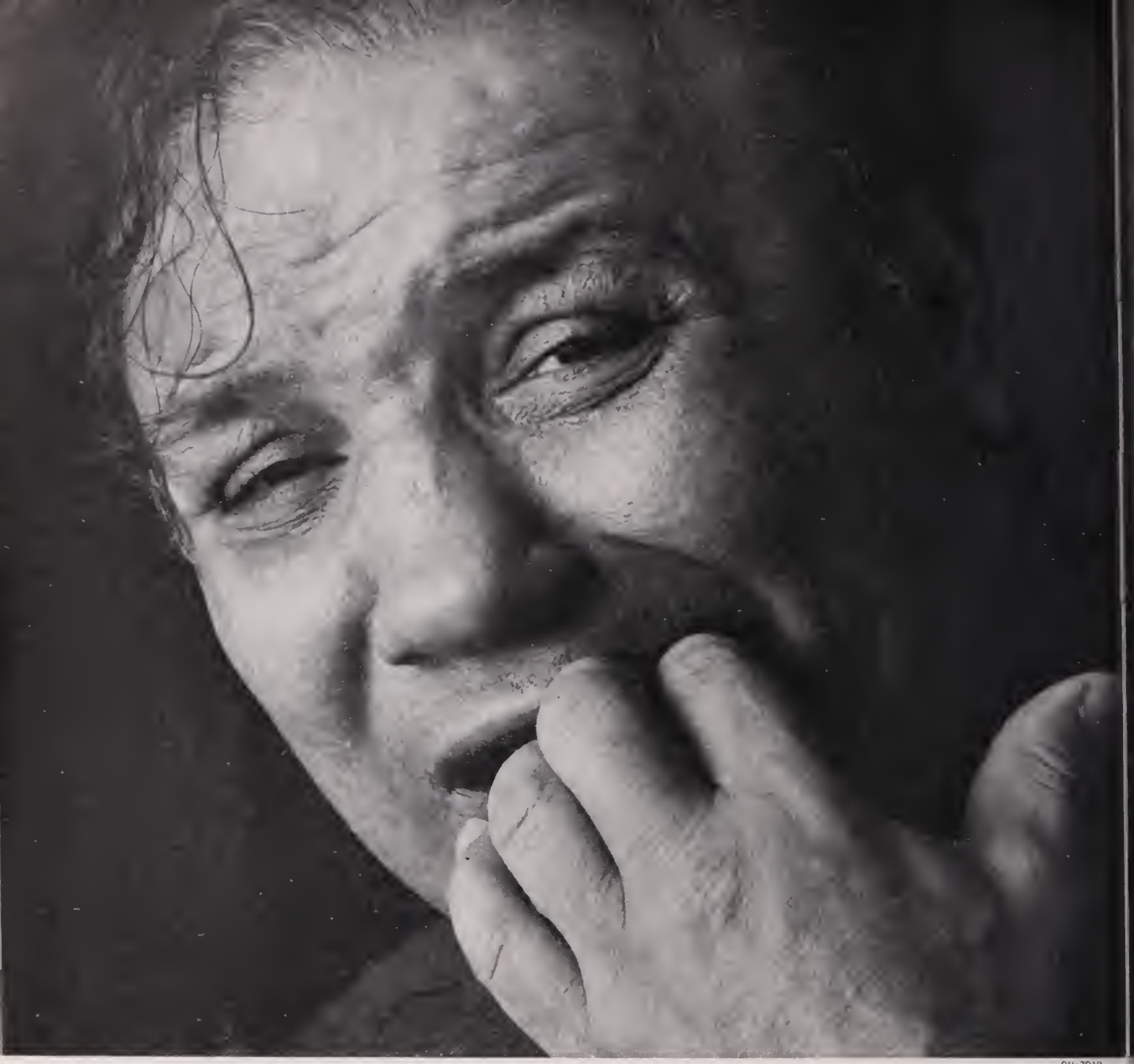
Medical Crisis?

THE SO-CALLED "crisis in our health-delivery system" has provided superlative material for political speeches, for eye-catching press headlines, and for demagogues who purportedly represent the poverty-stricken. I have asked myself many times: What are these crises in the world of medicine? I read in the morning newspaper that the gadfly of everything that is supposedly evil says that the medical profession should be "policed," that it does not merit the trust placed in it primarily because patients can not be sure of receiving competent care. The American Medical Association and physicians are portrayed as a most depraved organization and as conscienceless malefactors. It is alleged that the cost of medical care is outrageous, that the system for the provision of medical care is hopeless and that the pharmaceutical industry is overcharging the public.

I have three physician sons of whom I am very proud. Yet I sometimes wonder, were it possible to roll back the years, whether I would encourage them to embark upon a medical career, now that physicians and medical practice have been subjected to such vicious and seemingly concerted attacks. Maybe I am losing my tolerance of abuse and calumny, but it does seem to me that a headline catcher such as Ralph Nader's fulmination, which casts doubt on the judgment of good as well as poor physicians, without elaborating on how to implement the "policing" which he vociferously advocates accomplishes nothing except to destroy the confidence of the patient in his physician and to imbue the physician with helpless frustration indeed. No one, and least of all physicians, has ever said that the current scene in medical practice reflects "the best in the best of possible worlds." It is a quick and easy gibe, as spurious as it is flamboyant, to say that medicine costs too much and that hospitals are too expensive, without presenting some salutary alternative to the realities which must be faced and not dismissed with a cruel jest. There never has been a time when medical care could not be improved and when the lot of the poor did not need amelioration. It is also true that some physicians are less than altruistic and that some provide counsel and treatment which all of us would like to see infinitely improved. But we can say the same of any endeavor in all sectors of our society. Most practitioners of medicine probably would admit that the Ralph Naders amongst us do some good in that they constitute a voice exhorting us to do better. But shrill threats of policing, strident indictments of the American Medical Association on the charge that it is lethargic in response to the demands of social and economic progress, and massive verbal assaults upon all physicians without concomitant answers to complex questions involving feasible means of achieving constructive changes seem to me to represent chaos rather than useful order, and bedlam rather than efficacious counsel.

R. J. Jackman

President
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Interruption of the Hepatic Artery

Accidental in the Course of Portacaval Anastomosis

J. N. MAILLARD, M.D.*; M. HUGUIER, M.D.* and B. RUEFF, M.D.*

Summary: Traumatic thrombosis of the hepatic artery. No portacaval anastomosis. Un-

ACCIDENTAL INTERRUPTION of the arterial hepatic blood supply is seen mainly in the course of biliary surgery.[2] It is the purpose of this manuscript to analyze the particular problem such an accident poses for the surgeon on the occasion of portacaval anastomosis in a cirrhotic. The problem is illustrated by four personal observations.

Clinical Observations

First Observation (Figures 1 and 2)

On November 13, 1964, this 37-year-old woman with alcoholic cirrhosis was operated upon after three gastrointestinal hemorrhages within the previous 10 months. A portacaval anastomosis was planned. The portal blood flow was found to be 750 ml/min as measured by an electromagnetic flow-meter. The surgical dissection of the hepatic artery, for the purpose of measurement of its flow, caused a spasm which did not relent after periarterial sympathectomy. After removal of a thrombus from this artery, through a longitudinal arteriotomy, the opening was closed by a venous patch. The suture tore through one of the margins and the surgeon was obliged to resect the entire suture zone and proceed with end-to-end anastomosis after section of the gastroduodenal artery. In the course of these maneuvers a good retrograde blood flow was noted after removal of the clamp from the distal arterial segment. Because the hepatic artery was of small caliber and pulsated only feebly, the planned portacaval anastomosis was not done.

The postoperative course was uneventful. The laboratory findings were normal (Figure 1). On November 30, aortography demonstrated absence of arterial vascularization toward the liver (Figure 2). The patient was seen again after four months with another hematemesis, but moderate icterus and the general state of the patient precluded any surgical reintervention.

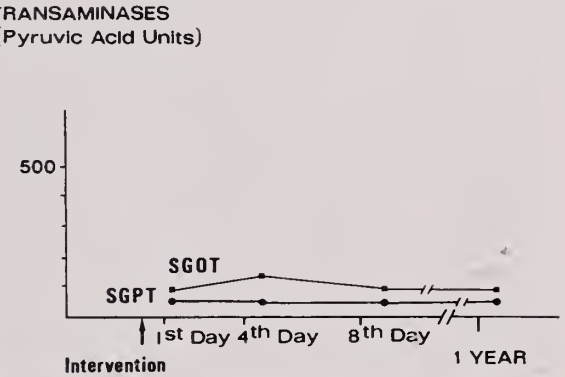


Fig. 1—Observation 1. Biological postoperative evolution.



Fig. 2—Observation 1. Postoperative aortogram. Interruption of the hepatic artery at the level of the first lumbar vertebra. Absence of arterial vascularization toward the liver.

*From the Clinique Chirurgicale de l'Hôpital Beaujon (Pr J. L. Lortat-Jacob) and Centre de Réanimation des Maladies du Foie et des Hémorraiges Digestives (Pr R. Fauvert), Hôpital Beaujon, 100 Bd du Général Leclerc, 92—Clichy—France.

eventful surgical recovery. Recurrence of gastrointestinal hemorrhages.

Second Observation (Figures 3 and 4)

This 56-year-old male alcoholic was hospitalized as an emergency case in June 1968 because of hematemesis. Hepatomegaly had been previously recognized and the gastrointestinal hemorrhage was attributed to rupture of esophageal varices. The laboratory tests for hepatic function were normal with the exception of coagulation time. (Quick = 50 percent). The splenic pulp pressure was 18.5 mm Hg. Three hours after the splenomanometry one could witness a rapidly developing shock which was compensated for by the transfusion of four units of blood. Splenectomy was performed 24 hours later because of the hemoperitoneum secondary to a splenic rupture. Despite the fact that hematemesis had stopped, the decision was made to supplement the splenectomy by portacaval anastomosis, in order to prevent an eventual spleno-portal thrombosis.

While dissecting the free border of the lesser omentum, the surgeon severed an artery, vascularizing the right hepatic lobe, which probably originated from the superior mesenteric artery. End-to-end suture was not possible because of the adiposity of the patient and the portal trunk was too short to permit arterialization of the distal segment. Because of the small caliber of the severed artery and because still another hepatic artery was perceived in the pedicle, an end-to-side portacaval anastomosis did not seem too hazardous, and was done.

The next day the patient was conscious. However, several parameters were disturbing: oliguria of 250 ml per 24 hours, tachypnea of 40 respirations per minute, tachycardia of 128 beats per minute and, above all, a considerable elevation of the transaminases (Figure 3). A ^{198}Au liver scan showed only faint radioactivity of the right lobe (Figure 4) compared to the left lobe. On the second postoperative day the transaminases decreased, but circulatory, renal and respiratory insufficiency remained. After 48 hours the patient became comatose and death ensued from collapse on the third day.

Necropsy showed hepatic cirrhosis with hemochromatosis. Almost the entire right lobe of the liver was infarcted secondary to ligature of a right hepatic artery. An arterial injection of barium demonstrated two hepatic arteries, a primary right and a primary left, both of them originating from the superior mesenteric artery, the left at the level of its origin and the right, one centimeter distally.

Summary: Splenectomy for traumatic hemoperitoneum. Accidental ligation of a right hepatic artery in the course of dissection of the portal vein. End-to-side portacaval anastomosis. Demise due to acute hepatic insufficiency after 52 hours. At autopsy an infarction of the right lobe of the liver was seen.

Third Observation (Figure 5)

This 56-year-old woman was hospitalized in May 1969 because of melena and ascites. There was a previous history of alcoholic cirrhosis and pre-pyloric ulcer. An upper gastrointestinal series showed esophageal varices and also confirmed the presence of the ulcer. For these reasons it was decided to perform both a gastrectomy and an end-to-side portacaval anastomosis at the same

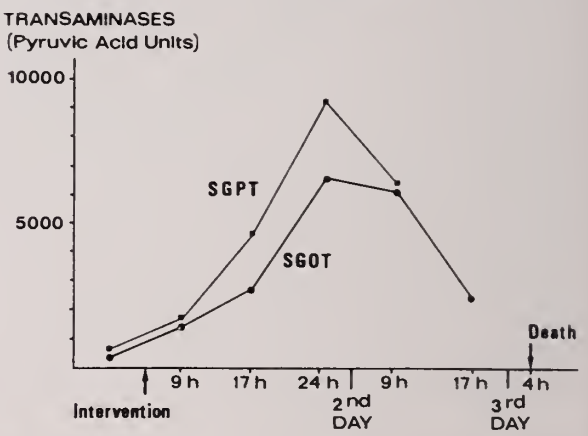


Fig. 3—Observation 2. Biological postoperative evolution.



Fig. 4—Observation 2. Postoperative liver scan with radioactive gold. The right lobe of the liver is only feebly visible.

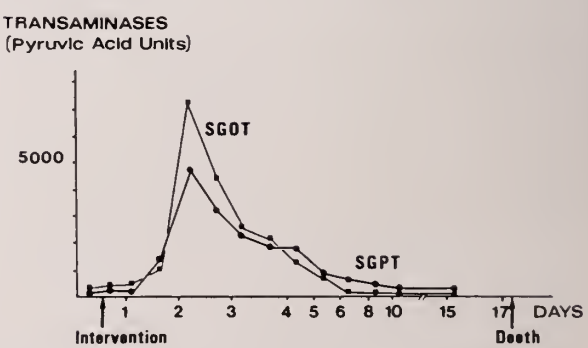


Fig. 5—Observation 3. Biological postoperative evolution.

time.

During operation on June 11, 1969, the upper part of the peritoneal cavity appeared uniformly covered with a mother-of-pearl shell. While dissecting the portal vein the surgeon ligated an artery, probably the right hepatic, together with retropedicular lymphatics. The peri-hepatitis did not permit observation of a possible color change of the liver. Arterialization of the distal segment of the portal vein appeared technically impossible. An end-to-side portacaval anastomosis, however, was performed and the previously planned gastrectomy undertaken, during which a duodenal ulcer, which had perforated in the hepatic pedicle, was removed.

Postoperatively a rise of the level of transaminases and a waking coma on the second postoperative day were observed (Figure 5). After several days the complications appeared to regress. On June 17 the patient was conscious again, and there were no more electrical signs of encephalopathy. However, she was icteric and anorexic. On June 21 there appeared a small leakage of the duodenal stump which was drained and irrigated with lactic acid. The condition of the patient deteriorated quickly and she died on June 29 in hepatic coma.

Necropsy showed a plastic peritonitis; the liver was cirrhotic with numerous necrotic nodules in both lobes. Arterial injections were not performed.

Summary: Accidental ligature of the right hepatic artery in the course of dissection of the portal vein. End-to-side portacaval anastomosis and gastrectomy according to Finsterer. Leakage of the duodenal stump and demise on the 18th postoperative day of hepatic coma. Necrotic nodules in both hepatic lobes.

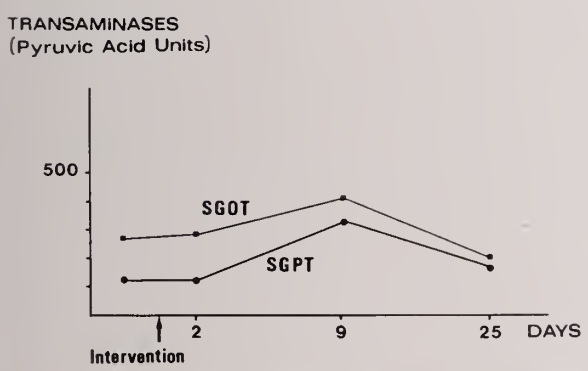


Fig. 6—Observation 4. Biological postoperative evolution.



Fig. 7—Observation 4. Postoperative coeliac axis arteriogram. The left hepatic artery originates from the left gastric artery. The portal trunk is opacified through the splenic artery. Along the right margin of the portal vein is seen a vessel which can be interpreted as a ligated right hepatic artery.

Fourth Observation (Figures 6 and 7)

This 47-year-old woman had been followed for two years because of a hepatosplenomegaly, portal hypertension, and biological syndrome of cholestasis suggesting primary biliary cirrhosis.

Operation was performed on May 18, 1968. The liver was cirrhotic and in the course of the dissection of the portal vein, a right hepatic artery was ligated on the right margin of the portal vein. The portal blood flow was 1000 ml/min. For this reason it was decided to combine the end-to-side portacaval anastomosis with an arterialization of the distal segment of the portal vein from the splenic artery. The flow through this anastomosis was 200 ml/min. The postoperative course was uneventful. Hepatic biopsy and the finding of antimitrochondrial antibodies by immunofluorescence confirmed the diagnosis of primary biliary cirrhosis. Portacaval anastomosis was undertaken because of a gastrointestinal hemorrhage.

Transaminase values were about 400 pyruvic acid units (Figure 6). After one month an arteriogram of the coeliac axis demonstrated good functioning of the arterio-portal anastomosis (Figure 7). The left gastric artery contributed a left hepatic branch. A vessel was demonstrated at the level of the porta hepatis which was not visible in the preoperative splenoportogram and which can perhaps be interpreted as the ligated trunk of the right hepatic artery.

Summary: Accidental ligation of a right hepatic artery in a course of dissection of the portal vein. End-to-side portacaval anastomosis and arterialization of the hepatic stump of the portal vein. Uneventful recovery.

Comment

Previous cases of accidental interruption of the arterial hepatic supply in the course of portacaval anastomosis have not been reported in the literature. Such an accident, however, represents a real risk. These four observations have been made in the course of a series

of 184 portacaval anastomoses between January 1964 and September 1969. The unnoticed ligation of a small hepatic artery could perhaps explain the transaminase increases following portacaval anastomosis, which have been reported in the past.

The spasm and thrombosis of a hepatic artery during dissection, in order to measure the blood flow (Observation 1), constitute a very unusual cause for the interruption of the arterial hepatic supply. The authors have since desisted from measuring the arterial hepatic blood flow.

The accidental ligation of a primary right hepatic artery in the course of dissection of the portal vein is a more common danger. This artery passes behind the base of the portal vein, then turns to its right side and reaches the hepatic hilus. Adachi, as cited by Couinaud,[3] has found such a primary right hepatic artery in 11 percent in a series of 252 cases. Twice it was the only hepatic artery. Fifteen times (5.9 percent) it was associated with the primary median artery; twice it was associated with the primary left hepatic artery; and finally it was associated 10 times (3.9 percent) with two other primary arteries, a median and a left one. The location and distribution of this artery is variable. Its accidental ligation can be explained in our observations by the absence of preoperative arteriographic documentation, and mainly by masses of hypertrophic and sclerotic lymph nodes at the base of the hepatic pedicle; the artery which runs through the middle of these masses can easily be ligated or severed in the course of the dissection of the lower part of the right side of the portal vein. If it crosses the portal vein higher up, it is much easier to identify. The frequency of this anatomic variation makes selective coeliac and superior mesenteric arteriography preferable to splenoportography in the assessment of portal hypertension.

In a patient with a normal liver an accidental ligation of the hepatic artery leads only infrequently to hepatic infarct.[2] In 19 observations, of which four were his own, Brittain[2] found only five hepatic infarcts in six deaths. In the majority of cases the oxygen supply by the portal veins is sufficient to assure viability of the hepatic parenchyma. In the cirrhotic patient the ligation of the hepatic artery has been utilized by Rienhoff[6] and Berman[1] in the treatment of some cases of ascites and/or gastrointestinal hemorrhage. Berman mentioned seven postoperative deaths in 23 patients with cirrhosis but he did not specify the cause of death. Six of Rienhoff's 21 patients died after arterial ligation; only two of the deaths were directly attributable to postoperative hepatic insufficiency. This complication must be considered in patients with cirrhosis accompanied by significant diminution of the portal flow. After accidental interruption of the arterial hepatic supply one should forego the intended portacaval anastomosis. The postoperative course would be uneventful; but the risk of gastrointestinal hemorrhage would persist.

Association of a ligation of the hepatic artery with portacaval anastomosis leads to variable consequences which, according to anatomic variances, however, can contribute to a rapid postoperative death. Popper[5] has shown in the normal dog, that ligation of the hepatic artery and of a part of the terminal branches of the portal vein leads inevitably to hepatic necrosis. The arterial collaterals are insufficient for an adequate oxygenation of the liver. In the first observation (Figures 1 and 2) the ligation of the right arterial branch caused massive necrosis as evidenced by repeated SGOT and SGPT elevation.[7] The necrosis of the right lobe of the liver has been confirmed by autopsy. Fatal hepatic insufficiency could not be prevented by arterial supply of the left lobe.

In the second observation the bilateral and limited character of the necrotic lesions makes one think, in the absence of anatomic certainty, that the ligated artery supplied the entire liver, but that the organ also was perfused from another source. The repeated transaminase values indicated a cytolysis of moderate intensity. The clinical course showed that acute insufficiency of the hepatic artery was not the only cause of death; another cause was a leakage of the digestive tract. It is difficult to know for sure whether the hepatic necrosis was an aggravating factor in the development of the duodenal fistula.

The clinical and experimental results suggest that in a case where one wants to perform a termino-lateral portacaval anastomosis even

after accidental interruption of the arterial hepatic supply, one should in addition perform an arterialization of the hepatic segment of the portal vein using the splenic artery according to the technique of Maillard et al.[4] The fourth observation (Figures 6 and 7) shows the possibility of accomplishing such an intervention with unremarkable clinical and biological consequences.

Conclusions

In the course of end-to-side portacaval anastomosis for portal hypertension due to intrahepatic block, it is possible to accidentally ligate a hepatic artery during the dissection of the portal trunk. Four such observations are reported. The small number does not permit definite conclusions; however, it invites the publication of other such recognized observations. The following remarks can be made.

1. It is possible that preoperative selective arteriography of the coelic trunk and of the superior mesenteric artery diminish that risk.

2. When a hepatic artery has been ligated, it seems reasonable to abstain from the planned termino-lateral portacaval anastomosis. If, however, one considers the latter indispensable, the authors suggest supplementing the procedure with arterialization of the distal segment of the portal vein.

Acknowledgment

Histologic studies were done by Drs. J. Barge and G. Molas. The arteriographies were performed by Dr. M. Levesque.

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Our Gold-headed Cane

The craving for magic and authority which is inherent in us all, especially when we are ill, has undoubtedly helped the doctor in the treatment of the patient. The gold-headed cane of the physician of the past became his rod of Aesculapius and when he cast it aside and tried to appeal to rational and scientific procedures he lost a powerful weapon. In no other way can I account for the fact that at a time when medical science has been advancing at a rate previously unknown, there is more scepticism and doubt as to the value of the services we render than ever before. Our patients may like us as individuals, but as a profession we have a "bad press."*

*Sir Walter Langdon-Brown: Thus We Are Men, 1969.

Editor's Note: I have a solid gold-headed cane with ebony stock (heirloom). Perhaps I should get it out.

First Come, First Served

The nurse motioned to one of the expectant fathers and announced, "You have a son." Another man dropped his cigarette, jumped up and cried, "Say, what's the idea? I was here before he was!"*

*Maxwell Droke: The Speaker's Handbook of Humor.

"The Man They Wouldn't Let Die"

"I am deeply honored for this award."

In clear English these were the words that came from the brilliant Russian physicist, Lev Davidovich Landau, on accepting the 1962 Nobel Prize in Physics in recognition of his "pioneering theories concerning condensed matter, especially liquid helium." Since Landau had been unable to go to Stockholm, Swedish Ambassador Sohlman had been delegated to present the prize to its recipient at the Hospital of the Academy of Sciences in Moscow.

What was so exceptional about this distinguished physicist that special note should be taken of his acceptance of his prize in person? The remarkable fact was that he was able to do so after nearly ten months of hospitalization and four "clinical deaths," from each of which he was retrieved by a team of persistent and dedicated doctors.

On January 7, 1962, after an automobile collision on one of Moscow's icy highways, Landau was brought unconscious to Hospital No. 50 with massive and multiple injuries, to wit:

Fracture of nine ribs, with piercing of the airtight membrane. On the left, a pneumothorax, with the lung totally collapsed and the pleural cavity filled with air. On the right, a hemothorax, with the lung partially collapsed and the lung membrane filled with blood. Rupture of the symphisis pubis, with resulting tears through the abdominal organs. The pubis, ischium and ilium apparently broken, also the left femur.

"The scientist was dying."

Why didn't he die completely? Only because the medical "brain trust" at his bedside was stubbornly determined to reverse the process.

Nevertheless, on January 11, despite phenomenally heroic measures, the spark of life wavered and went out. "Landau had entered the state of 'clinical death.' His first death—but not his last."

Thrice more, on January 12, 16, and 18, seemingly invincible complications set in and Landau "died"—to be again rescued from the proverbial jaws of death by the herculean efforts of doctors, nurses, and attendants, all of whom resolutely refused to capitulate.

Finally, after weeks of cheating the Grim Reaper, Landau was out of danger but still for the most part immobile, speechless, and unresponsive. On April 8 he uttered his first word: "Spasibo" ("Thank you") when a nurse held to his mouth a rubber-nippled bottle of water. From then on recovery was long, slow, tedious, and only partial, plagued with intractable "phantom" pain.

Landau returned home in January 1964, two years after the accident.

* * * *

The prodigious application of instrumental contrivances and the sequence of graphic but grim procedures employed to maintain and finally stabilize the flickering spark of life cannot be catalogued here. For the incredible and arresting details of this gripping story the curious are referred to Alexander Dorozynski's "The Man They Wouldn't Let Die," MacMillan Co., N. Y., 1965.*

*With acknowledgments to and quotations from Alexander Dorozynski: The Man They Wouldn't Let Die, 1965.

Today a dollar earned is a nickel saved.—Herbert Prochnow

Portal Vein Thrombosis in Intrahepatic Block*

C. SICOT, M.D.; D. SAKELLARIDIS, M.D.; B. RUEFF, M.D.;
J.-N. MAILLARD, M.D. and J.-P. BENHAMOU, M.D.†

THE COMBINATION of intrahepatic block and portal vein thrombosis raises difficult diagnostic problems and generally renders portacaval anastomosis impossible. Therefore it seems worthwhile to describe our experiences with 13 cases in which this combination was encountered.

Materials and Methods

Between 1952 and 1968, 250 adult patients with portal hypertension due to intrahepatic block were selected for portacaval anastomosis. In all cases histologic confirmation of the hepatic lesions was available from surgical biopsy, and information on the state of the portal vein dynamics by direct surgical exploration. The trunk of the portal vein was found to be completely thrombosed in 13 patients. Patients with partial thrombosis of the portal vein were not included in the study; neither were those with portal vein occlusion secondary to surgical portacaval anastomosis.

Results

The nature of the hepatic process in the 13 patients with complete portal vein thrombosis, their clinical condition, the findings at splenoportography and ileoportography, and the attempted treatment are shown in the Table.

Six patients had had previous splenectomy. The interval between splenectomy and the detection of portal vein thrombosis ranged from 15 days (Patient 5) to 31 years (Patient 12). In Patient 5 splenectomy had been performed because of rupture of the spleen following splenoportography; splenoportography had shown an apparently normal and patent portal trunk, yet two weeks after splenectomy, during an operation for portacaval anastomosis, the portal vein was found completely blocked by a thrombus.

Splenoportography was performed in six patients. It revealed a hepatopetal collateral circulation in only one. In five patients the portal vein was not visualized; in the sixth case (Patient 8) it appeared normal, and it is likely that the thrombus had formed during the two weeks intervening between splenoportography and operation. Ileoportography performed during operation in seven patients revealed hepatopetal collateral circulation in all seven, but in no case an opacification of the portal trunk.

Discussion

In this series the incidence of portal vein thrombosis in portal hypertension due to intrahepatic block was 13 out of 250, or 5.2 percent, which corresponds to the lower range of the incidence in most other series[4,7,10,17] where it was reported between 5 and 11 percent. The difference may reflect the fact that our patients were not a representative sample of sufferers from portal hypertension due to intrahepatic block, since they had been especially selected for portacaval anastomosis. Moreover, they were studied at a given point of their illness. Incidence rates of portal thrombosis obtained in this type of patient are bound to be lower than those based upon postmortem data, which reflect the total evolution of the disease.

Diagnosis

The diagnosis of portal vein thrombosis in a patient who already has an intrahepatic block is difficult. Sudden or rapid increase of the manifestations of portal hypertension is a significant sign,[20] but is not always present. Abdominal pain and/or bouts of fever may occur but are atypical and inconstant.[17] Intestinal

*See editorial, page 129.

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TABLE

Portal Vein Thrombosis in Portal Hypertension due to Intrahepatic Block: Analysis of Data in 13 Patients

Case No. and liver affection	Sex, portal thrombosis detected: Age (years) and year	Splenomegaly	Year of splenectomy	Ascites	Splenoportography: Portal trunk	Splenoportography: Hepatopetal collateral circulation	Ileoportography: Portal trunk	Ileoportography: Hepatopetal circulation	Operation: Portal trunk	Operation: Treatment	Course
1 Cirrhosis + hepatoma	F 60 1962	±		+	Not visualized	—			Thrombosed	PCA† after thrombectomy	Death 8th postop. day #
2 Cirrhosis + hepatoma	M 68 1963	—		—	Not visualized	—			Thrombosed	—	Death 4th postop. day #
3 Cirrhosis + hepatoma	M 48 1967	+		+	Not visualized	—			Thrombosed	—	Death 7th postop. day #
4 Cirrhosis + hepatoma	M 70 1968	+		+					Thrombosed	—	Death 4th postop. day #
5 Cirrhosis	F 46 1961		1961	+			Not visualized	+	Thrombosed	—	Death 2nd postop. month (gastrointest. hem.)
6 Cirrhosis	M 17 1957		1956	±			Not visualized	+	Thrombosed	Esophagogastric resection	Death 14th postop. day (disruption of anastomosis)
7 Cirrhosis	M 55 1967		1958	—			Not visualized	+	Thrombosed	CMA‡	Death 18th postop. month §
8 Cirrhosis	M 60 1963	±		+	Patent*	—			Thrombosed	—	Death 24th postop. hour (cardiac arrest)
9 Cirrhosis	M 47 1966	±		+	Not visualized	+			Thrombosed	—	Death 3rd postop. month (gastrointest. hem.)
10 Cirrhosis	M 54 1967	—		+	Not visualized	—	Not visualized	+	Thrombosed	CMA‡	Death 6th postop. day ¶
11 Congenital hepatic fibrosis	M 54 1962		1931	+			Not visualized	+	Thrombosed	—	Death in 1964 (cachexia)
12 Congenital hepatic fibrosis	F 54 1964		1933	±			Not visualized	+	Thrombosed	—	Death in 1965 #
13 Hepatoportal sclerosis	M 28 1965		1955	±			Not visualized	+	Thrombosed	—	Death in 1968 (volvulus of small intestine).

*See under results
†Portacaval anastomosis (end-to-side)
‡Caval-mesenteric anastomosis (end-to-side)
#Massive gastrointestinal hemorrhage.
§Subacute glomerulopathy. No recurrence of gastrointestinal hemorrhage.
¶Syndrome of ligation of inf. vena cava.

infarction is a recognized, though rare, complication of portal thrombosis; however, it is associated with massive thrombosis of the portal vein in one of every two cirrhotic patients in whom it does occur.[6] Splenoportography fails to be an essential diagnostic tool, since it does not visualize the portal vein in about 10 percent of cases of intrahepatic block with an anatomically patent portal vein.[2] Thus in cirrhosis spurious portal thrombosis is seen four times more frequently than true portal thrombosis.[2,3]

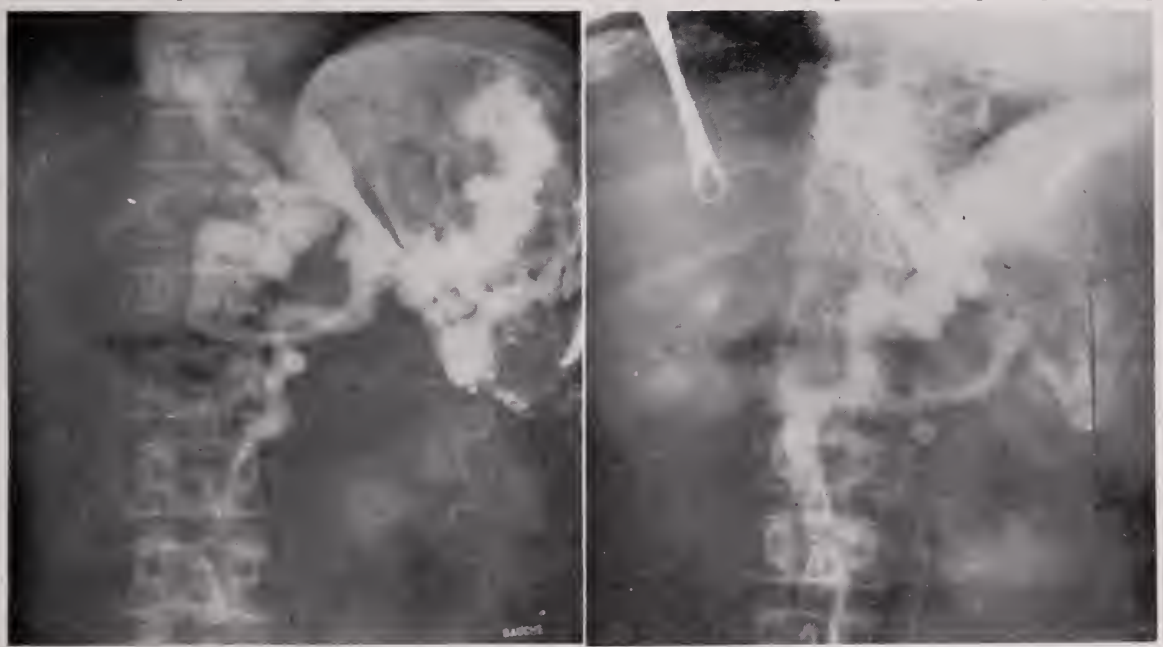
Non-opacification of a patent portal vein by contrast material during splenoportography is due either to reversal of portal venous blood flow[12,16,19,11] or to the presence of two currents within the portal system, one fed from the splenic vein and draining into an enlarged left gastric vein, the other fed from the mesenteric vein and draining into the portal vein.[2] This may explain the reason why spurious thrombosis is more rarely encountered with ileoportography than with splenoportography, although even in the former it is not exceptional. In one of our cirrhotic patients, in whom portal vein thrombosis was diagnosed because the portal vein was not visualized either by splenoportography or by ileoportography, necropsy disclosed an anatomically patent vein (Figure). Non-visualization of a portal vein by ileoportography can thus not be regarded as absolute evidence of portal vein thrombosis.

Hepatic Disease

The hepatic diseases in this series were: cirrhosis, cirrhosis with hepatoma, congenital hepatic fibrosis and hepato-portal sclerosis. Their distribution in our 13 patients with intrahepatic block and portal thrombosis is approximately the same as that found in patients with intrahepatic obstruction without portal thrombosis,[13] except that in our group the incidence of cirrhosis with hepatoma appears unusually high, hepatoma being present in four of our 10 cases of cirrhosis, whereas the incidence of hepatoma in cirrhosis is on the order of 6 percent in France.[1] In cirrhotic patients with hepatoma, portal thrombosis occurs secondary to invasion of the portal vein by the neoplasm. Portal vein thrombosis has been reported in patients with intrahepatic block from other causes than those observed in our series, such causes include schistosomiasis,[5] syphilitic involvement of the liver,[7] and partial nodular transformation of the liver.[18]

Precipitating Cause

Splenectomy, which had been performed in six patients of our series, appears to be a frequent precipitating cause of portal vein thrombosis, whenever an intrahepatic portal block exists and probably occurring very soon after the operation. In Patient 5 the portal vein, which had been patent at splenoportography



Figure—Spurious portal thrombosis in a patient with alcoholic hepatic cirrhosis (A-left)—splenoportography. (B - right)—ileoportography. Necropsy revealed a patent portal vein.

prior to splenectomy, was found completely thrombosed at re-operation two weeks after splenectomy. Isolated splenectomy should be avoided in patients with portal hypertension due to intrahepatic block. It may well be that ileoportography or, in fact, any procedure interfering with the portal system is likely to provoke thrombosis of the portal vein. There is a case on record of superior mesenteric thrombosis following ileoportography in portal hypertension due to congenital stenosis of the portal trunk.[14] It would seem reasonable to assume that thrombosis may also follow these investigative procedures in portal hypertension due to intrahepatic block.

Apart from splenectomy and from extension of hepatoma into the portal vein, no specific cause for portal vein thrombosis was found in this series. One might assume that portal hypertension resulting from intrahepatic block had led to changes in the vessel walls. This has actually been reported in hepatic cirrhosis.[9] These changes of the wall of the portal vein appear to be particularly common in hepatoportal sclerosis, where they may even precede the hepatic lesions.[15]

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Summary

Portal vein thrombosis occurred in 13 of 250 patients with portal hypertension due to intrahepatic block, who had been selected for surgical portacaval anastomosis. In four patients the portal thrombosis was due to hepatoma invading the portal vein, in six to previous splenectomy, and in three the cause could not be established. The diagnosis of portal thrombosis is difficult in the presence of intrahepatic block. An anatomically patent portal vein may not be visualized by splenoportography or even by ileoportography.

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Learning

We should live and learn; but by the time we've learned, it's too late to live.—Carolyn Wells

Acute Comatose Hepatitis*

Symptomatology and Natural Course

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SINCE 1966 THE TREATMENT of grave hepatitis has commanded renewed interest. Some diagnostic confusion and an often incorrect appreciation of the natural history of the disease has rendered the judgment of various therapies quite difficult. For this reason the authors have undertaken a precise outline of the symptomatology of acute comatose hepatitis and its natural course. This pursuit is based in part on reports in the literature[8,25,26,34] and, on the other hand, on personal experience with 87 cases, including 76 of viral hepatitis, eight of mushroom poisoning, one of phosphorus poisoning, and two of drug-precipitated cases of hepatitis (one case due to phenylbutazone, one to halothane).

Hepatic Encephalopathy

Hepatic encephalopathy is not much different from that encountered in cirrhotics. However, intensive observations in a specialized center of resuscitation have permitted us to formulate certain diagnostic criteria of hepatic coma (Stage III).

Stage I

The first stage is characterized by neurologic signs, especially asterixis. This is often of very short duration and frequently can be ascertained only by interrogation of the patient's family or close associates (difficulty in walking or keeping the bed covers on).

Stage II

The second stage, psychic disorders, is the most common and is characterized by somnolence in daytime alternating with nocturnal insomnia. In this stage of the disease the patient can be aroused; however, he is confused and disoriented as to time and location. There is often asterixis and alternating general hypotonia and extrapyramidal hypertonia. The somnolence of the patient deepens and he slips into an agitated coma with moaning and sometimes even shouting. By the time the patient progresses from Stage II to Stage III restraint or sedation is often required.

Stage III

The third stage is always coma, which evolves in a rather stereotype fashion. At first the coma is agitated, not very deep, and often associated with an extrapyramidal hypertonia, which varies from one moment to the next. It involves the arms and the masseters, as well as the erector trunci; in certain cases one can notice nuchal rigidity, even opisthotonous[11] one personal observation). Deep tendon reflexes are present. The Babinski sign is not constant, but in about one half of the cases it may be positive bilaterally or unilaterally, varying from time to time. Pill-rolling movements of the hands are almost always observed at this stage, either spontaneously and by themselves, or accompanied by spontaneous hyperventilation; sometimes they can be elicited by painful stimuli. They do not have the significance of decerebration.[16] The pupillary light reflexes and coronary reflexes are present, ventilation is spontaneous, and the cough reflex is not suppressed.

Deep Coma

There is general hypotonia. The Babinski reflexes are indifferent but the deep tendon reflexes begin to disappear progressively. For a long time the respirations remain spontaneous. Assisted ventilation becomes necessary when one observes either respiratory pauses or marked hyperventilation (two personal observations

*A substantial part of this paper was presented at a meeting on resuscitation at the Hôpital Claude Bernard, Paris (31).

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of death, probably by apnea). Involuntary movements are frequent: rhythmic fluttering of one eyelid, chewing, and hiccups. Then the corneal reflex begins to disappear. Spontaneous ventilation and the pupillary light reflexes persist the longest.

Frequently one observes *focal convulsions* (one arm, one side of the face, one side of the body) which alternate in time and location.[1,19] These convulsions are observed frequently and in our experience occur in about 50% of the cases. Initially of short duration they recur in ever decreasing intervals. Several times the authors have observed bouts of Jacksonian epilepsy which lasted anywhere from one to 12 hours. The blood sugar is normal during these convulsive episodes; on the other hand we have not been able to observe a convulsive crisis during 10 hypoglycemic episodes. This type of crisis ends suddenly and leaves the patient in a death-like coma which occurs either gradually or after a Jacksonian epileptical state, following a prolonged period of hyperventilation, cardiovascular shock or hyperthermia; or a combination of these. There is a general hypotonicity of the muscles without spontaneous movement or reaction to stimuli.

The deep tendon reflexes, cutaneous and light *reflexes have disappeared*. Spontaneous respiration has stopped. The electrocardiogram remains flat. On two occasions the authors have observed a polyuria with a urinary specific gravity of 1.001 which could be controlled by posterior pituitary extract. In one patient who apparently had progressed to a death-like coma, the authors could observe a temporary reappearance of the deep tendon reflexes. The central spinal fluid is normal[1] and the authors have not observed any case of subarachnoid hemorrhage.

The abnormalities of the electrocardiogram are identical to those of the encephalopathies of the hepatic cirrhosis[1,7,12] They are of considerable diagnostic interest because they are present from Stage I and very useful in observing the progress. The electroencephalographic tracings which were repeated several times during the 24 hours after coma show monomorphic delta and/or permanent triphasic waves; alternating showers of regular delta waves and phases of slow and less defined ones; progressive flattening and slowing of the tracing; and disappearance of reaction to noise or painful stimuli. It is important to realize that these different aspects can alternate at any time. Peaked waves of low voltage or ill-defined waves may precede or accompany convulsions, and are often followed by a period of electric silence which is usually terminal.[13]

Clinical Signs of Hepatic Failure

Jaundice

There is always jaundice. Usually it is present before the encephalopathy occurs; occasionally it can occur after the appearance of encephalopathy and sometimes simultaneously. The longer the duration the more intense the jaundice. It does not subside prior to death as one classic publication states.[22] The liver is typically small, the inferior edge cannot be palpated, and the total hepatic dullness is also reduced and sometimes entirely lost. In such cases the hepatic outline can still be demonstrated either by abdominal roentgenogram or by a liver scan.

Ascites

In 10% of the cases one can observe ascites; this is particularly true whenever the course of the disease is prolonged. The ascites can be abundant (in one case more than 4 liters). It can exist without any sign of cirrhosis. The fluid has a low protein concentration and the cell count is unremarkable in the absence of secondary infection. This ascites appears to be the result of sodium retention and accompanies a relative oliguria, positive water balance, weight gain and moderate hyponatremia (130 mEq/L).

Pain

In mushroom poisoning the syndrome is constantly associated with pain over the liver, sometimes the first sign of the poisoning. In cases of viral hepatitis, it is perhaps the reason why the patient moans and one can actually observe pseudo-surgical "acute abdomens."[23,30]

Spider angiomata are infrequently noted.

Foetor hepaticus is encountered in about two thirds of the cases.

Laboratory Findings

Liver Enzymes

There are constant but variable increases of SGOT and SGPT. Studies of other liver enzyme tests did not single out any one particular enzyme which might be more useful.[8] In a group of patients with toxic hepatitis we find a very good correlation between the serum concentration of the enzymes and the degree of hepatocellular insufficiency due to hepatic necrosis.[32]

Serum Bilirubin

Total serum bilirubin is usually about 20 mgm/100 ml., and 80% of it is conjugated bilirubin. The alkaline phosphatase may be moderately increased.

Maclagan Reaction

In severe viral hepatitis the Maclagan reaction is usually positive (in 27 of 33 cases above 20 Vernes units); but it is normal in severe toxic hepatitis (one case of phenylbutazone, one of probable halothane poisoning).

Cholesterol

Serum cholesterol is decreased, but the values show wide variations. They are 100 mgm/100 ml or less in 20 of our 47 cases. The esterified fraction can be very low, moderately decreased or normal. After the illness has been present for several days, it is not exceptional to see an increase.

Albumin

Serum albumin concentration is variable and, since the disease often occurs suddenly in a previously normal individual, it is frequently normal. It is decreased if the patient had been subject to a chronic disease with malnutrition or if hemodilution of several days exists.

Ammonia

The arterial blood ammonia is always above 100 mcgm/100 ml. In a given patient it varies from day to day without any relation to the clinical course or condition.

Colloidal Gold

The fractional colloidal gold clearance was determined three times and was once moderately diminished and twice normal.

Problems of Hemostasis

Habitually one characterizes the picture of severe hepatitis by the triad of icterus, coma, and diffuse hemorrhages.[8] As a matter of fact, in our experience cutaneous and mucous hemorrhages are constantly present (petechiae, ecchymoses, bleeding of the pharyngeal mucosa). But there is no oozing from wounds. Gross hematuria occurs only exceptionally. Gastrointestinal hemorrhages are frequent but not exsanguinating. If the gastric aspirate is observed over the 24-hour period, one can observe coffee-ground fluid alternating with clear liquid gastric content. Melena is unusual. Autopsy does not disclose large quantities of blood in the gut, so that diffuse hemorrhage does not seem to be the rule.[19] As a matter of fact, hypercoagulability has been observed repeatedly with thrombosis within an arteriovenous fistula.

Nevertheless in some of the rarer cases we can encounter severe hemorrhages. Two pregnant women in a group of 87 patients had aborted spontaneously with consequent uncontrollable hemorrhage. Otherwise, severe and uncontrollable gastrointestinal hemorrhage could be observed only four times. Necropsies did not show a true ulcer, but only superficial mucosal ulcerations or just gastric mucosal petechiae.

Disorders of the clotting mechanism are rather complex. Hepatic cellular necrosis is responsible for diminished synthesis of some coagulation factors which are normally synthesized by the liver: prothrombin (factor II), proaccelerine (factor V), proconvertine (factor VII), Stuart factor (factor X), and antihemophilic factor B (factor IX); the greater the hepatic necrosis, the smaller their plasma concentration, less than 10% of normal in the majority of our cases. The highest concentrations do not exceed 30%. The fibrinogen concentration is diminished but only exceptionally lower than 100 mgm/100 ml. After a duration of several days of the disease one can regularly observe a decrease of platelets, sometimes to the proportions of a pertinent thrombocytopenia. Paradoxically, all these defects together rarely result in a hypocoagulability which is demonstrable in vitro.

Whereas in the course of cirrhosis one can classically observe a primary fibrinolysis, this phenomenon has not been found in severe acute hepatitis. On the contrary, one frequently notices intravascular coagulation with secondary fibrinolysis.

Defects of certain coagulation factors and the presence of intravascular coagulation make therapeutic decisions very difficult. In fact, massive substitution therapy of the various coagulation factors and fibrinogen may aggravate the intravascular coagulation process considerably. On the other hand, the administration of heparin to these patients is likely to provoke a syndrome of general hemorrhage. In most cases it seems justified to avoid both types of therapy. However, treatment with a combination of the two might be undertaken in unusual circumstances under the control of a specialized laboratory.

Changes in Ventilation and Acid Base Balance

Hyperventilation

Hyperventilation has been observed in severe hepatitis as well as in severe cirrhosis.[4,35] It is constantly present in the experience of the authors. Sometimes it appears as a tachypnea, sometimes as a hypercapnea without increase in the frequency of respirations.

Hypocapnea

There is always a hypocapnea (pCO_2 smaller than 35 mm Hg in 27 out of 38 patients). It can be very severe: smaller than 30 mm Hg in 21 out of 27 cases and smaller than 20 mm Hg in six out of 27 cases. When hypocapnea is absent, its absence can always be explained either by an obstruction of the superior airways (in this case hypocapnea will occur after intubation) or an associated condition which depresses the ventilatory center (in our experience this happened in two jaundiced patients with barbiturate poisoning).

Plasma Bicarbonate

Plasma bicarbonates are irregularly decreased. In two cases, they were markedly so with an acidosis (pH 7.04 and 7.10). In four cases they were decreased enough to account for a normal pH. In 14 cases we found an alkalosis (pH above 7.45), very severe in eight cases where the pH exceeded 7.5; in one patient it exceeded 7.6 In these 14 cases plasma bicarbonates were either normal or moderately decreased. In several cases the authors observed a progressive increase of the plasma bicarbonate until abnormally high values were reached (30 mEq/L and more) in the absence of alkali therapy, continuous gastric aspiration, or therapy with adrenal corticosteroids. The pH of the urine ranged from 5 to 6.

Cardiovascular Findings

Severe hepatitis is usually associated with tachycardia.[8,19] The blood pressure is generally low. Hemodynamic studies by the authors in 16 patients have revealed the following facts: (a) in five patients the cardiac output was found to be normal (5.9 L/min $\pm$ 1.2) and increased in 11 others (in five of these it exceeded 10 L/min in 7 measurements). This increase of cardiac ouput cannot be related to fever, hypoxia, or convulsions. There is always hypocapnea. (b) Cardiac output is elevated and the peripheral arterial resistance is lowered (849 ± 232 dynes/sec/cm^{-5}); it was also low in two patients with a normal cardiac output. This defines a circulatory hyperkinesia which is well known in cirrhotic patients[18,28] and has also been described in several cases of severe hepatitis.[14,28] In one patient we have observed sinus bradycardia of less than 40 beats per minute, which could be accelerated by atropin or isoproterenol.

Several times we have noted episodes of profuse perspiration in the absence of fever, hypercapnea or hypoglycemia.

Comments re Symptomatology

The symptomatology of severe hepatitis includes cholestasis, hepatic encephalopathy, complex defects of hemostasis, hyperventilation and circulatory hyperkinesia. These symptoms must be concomitant with acute hepatocellular disease for which one has to add the following criteria: (a) elevation of serum transaminases, (b) the absence of previously existing liver disease or the certainty of an acute pathologic episode.

Short increases of serum transaminases can be observed in certain cases of congestive fail-

ure,[2,9] and even more rarely in cases of cholestasis.[8]*

The association of neuropsychiatric symptoms and icterus is not sufficient for the diagnosis. Neither the asterixis[15] nor the electroencephalographic changes[12] are pathognomonic for severe hepatic insufficiency. Coma in an icteric patient may be due to coincidence: to post-epileptic coma[20] or to personally observed cases of barbiturate poisoning. The association of jaundice and psychiatric signs is also frequently observed in patients who are severely ill, either postoperatively or with severe septicemia.

The abnormalities of hemostasis are difficult to interpret. The frequent observations of disseminated intravascular coagulation should make one very cautious in the interpretation of laboratory findings concerning hemostasis and coagulation.

Hyperventilation and circulatory hyperkinesia has been encountered in the course of certain gram-negative bacteremias.[33,36]

Course and Prognosis

Mushroom Poisoning

In mushroom poisoning the icterus appears on the third day after ingestion and increases daily thereafter. Encephalopathy appears on the fourth day, and coma on the fifth. The course is variable, according to the seriousness of the intoxication. In our experience we have observed three recoveries of eight cases of coma which lasted from three to 12 hours.

Viral Hepatitis

Characteristically, the neuropsychiatric signs in viral hepatitis appear either simultaneously with the appearance of the icterus (fulminating hepatitis) or after a course of about three weeks (secondarily aggravated).[8,26] Rarely may the encephalopathy actually precede the icterus.[19] Caroli and Hecht[11] distinguish three types. The fulminating hepatitis appears suddenly, develops rapidly, occurs in young subjects and is always fatal. The aggravated hepatitis makes its appearance in the second week of the jaundice, the course is slow, and the patient can recover (four out of seven patients). The severe slow hepatitis is usually seen in older patients; it was fatal in two cases out of four, but for reasons other than hepatic coma. Thirty-five of our 45 patients had a fulminating form of hepatitis. The ages varied (14 patients under 30 years; four over 60 years; two were 75 years old); six of seven recoveries belong to this group. Eight of our patients had a secondarily aggravated form of hepatitis; on the average they were older and none of them recovered. Only two patients experienced an aggravation in the second week; one of them (aged 35) recovered.

The Fatal Forms

There were 62 cases of infectious hepatitis, six of toxic hepatitis, and one of drug hepatitis. The course of these forms is rather schematic. In the actual practice and opinion of the authors the life span of these patients depends on the circulatory state and neuropsychiatric signs.

The circulatory state of these patients is critical. In one study of 16 patients, the authors have observed 40 episodes of cardiovascular collapse and two of cardiac arrest which recovered under external cardiac massage. Hemodynamic studies have shown that there is a first phase consisting of a syndrome of circulatory hyperkinesia with decreased venous pressure: a condition which can be partially corrected by sufficient administration of fluids (1-2 L/24 h). This stage of increased cardiac output is followed by circulatory insufficiency in which we find the cardiac output diminished and the venous pressure elevated.

The neuropsychiatric state of these patients is the second critical factor. The most often observed course is the development of coma, either gradually or suddenly after a convulsive seizure, sometimes associated with a fever of 40°C, hyperventilation, cardiovascular collapse, or hypoglycemia.

The circulatory and neuropsychiatric symptoms are often so interconnected that they are hard to distinguish. Thus "decerebration" and cardiovascular shock often occur simultaneously; in two patients of the authors' own series coma began immediately after cardiac arrest. Other developments can be observed:

Hypoglycemia occurs frequently in a course of severe hepatitis. It is correctible by continu-

*The acute Budd-Chiari syndrome can show a similar picture of acute severe hepatitis.[6] Though not discussed here, it has the same physiopathologic significance.

ous intravenous administration of 9 gm of glucose/hr (administered by a separate vein).

Apnea has been noted twice in one patient and should be avoided by assisted ventilation.

Fever of 40°C can be observed in the absence of infection. It greatly aggravates the cardiovascular burden and must be corrected. The risk of infection is ever present in those patients who have an urethral catheter, endotracheal tube, two or more intravenous infusions simultaneously and sometimes an arteriovenous shunt. The authors have monitored bacteriology systematically by taking blood cultures whenever the patient's temperature rose above normal, and by culturing all the material obtained from the patient until his demise. Two septicemias (E. coli and Serratia) were definitely established in a group of 25 patients. Staphylococcus albus was found on the catheters of five patients, and enterococcus and/or E. coli were found simultaneously on five catheters.

Massive, fatal hemorrhages are rare but were observed in six of a group of 69 patients (two uterine hemorrhages and four intestinal hemorrhages).

The Forms of Hepatitis which go on to Recovery

The occurrence of spontaneous recovery in the absence of any treatment in grave hepatocellular insufficiency is known.[19,21,24,37] The authors have observed 18 similar cases (14 infectious hepatitis among 76, three mushroom poisoning among eight, and one drug hepatitis in two).

By the time neuropsychiatric signs appear, the individual patient does not differ greatly from the group who go on to die. The duration of the coma is from several hours to five days. In one case the spontaneous development of pill-rolling motions was observed. Hyperventilation is always present. Two of the patients had to be intubated; and in two, tachycardia was noted in the absence of fever or convulsions. The liver was small in two of the patients, and in one of them the hepatic dullness measured only 3 cm in the mammary line. Total serum bilirubin was always below 20 mg/100ml. The coagulation time after Quick was less than 25 percent of normal in four patients, and in two patients with mushroom poisoning the concentration of proaccelerine was less than 10 percent of normal. In a woman of 60 years, the authors observed a viral hepatitis, which became secondarily aggravated and went into coma within 30 hours, in which, however, plasma prothrombin and ammonia were almost normal. Liver biopsy by Menghini needle showed a moderate hepatic necrosis. This observation resembled the data which were observed by Laverdant and Bernard.[23a] These authors observed 12 patients with viral hepatitis, cardiovascular collapse, and/or hyperventilation and/or hyperthermia and/or neuropsychiatric symptoms without gross disturbances of laboratory findings relating to hepatitis, particularly without prolongation of prothrombin time. Six of those 12 patients died.

Discussion of Prognosis

The following are the criteria for the fatal character of a severe hepatitis:

1. Encephalopathy preceding the jaundice.
2. Fulminating hepatitis.[11]
3. Disappearance of the hepatic dullness.
4. Pill-rolling movements of the hands.[5]
5. Plasma proaccelerine lower than 10 percent of normal.[10]
6. Total bilirubin over 20 mg/100 ml.[17]

The authors have actually observed patients who recovered, although they had one or the other of these signs, isolated or associated. It is the impression of the authors that the mortality of grave hepatitis varies in time and location as the experience of Gaubert and Carayon and Reynolds suggest.[20,29] On the other hand, they described important variations in their experiences in groups of patients who appeared comparable in disease as well as in the treatment received.

The majority of the observations which are used in this report were made in the service of Professor R. Fauvert, in collaboration of Annie Elman, Denise Friedler, Michele Pagniez, Francoise Verdier, C. Abramowitz, P. Berthelot, J.-M. Desmonts, D. Dhumeaux, P. Dupuy, S. Erlinger, G. Feldmann, P. Glaser, J. Hakim, O. Hoanca. One of the observations originated from the service of Professor Domard. Two observations involving children came from the service of Professor Julien Marie in collaboration of Doctors Cloup and Feron. The eight patients with the mushroom poisoning were followed in the services of Professors M. Gaultier, S. Thieffrey and M. Goulon in collaboration with Chantal Bismuth, Annie Barrois, J.-P. Frejaville, J.-B. Jolly and G. Huault.

Coagulation studies were done by Doctors Doris Menache and Marie-Claude Guillin.

The electroencephalographic studies were performed by Doctor Regine Cloche.

References may be secured from the author or the reprints.

The Acute Budd-Chiari Syndrome*

Clinical and Biological Aspects of Two Observations

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JEAN-NOEL MAILLARD, M.D.†

By classification there are two types of the Budd-Chiari syndrome. One of them is subacute and often results in nodular regeneration, creating clinical, biological and hemodynamic aspects of cirrhosis. The other type is very acute and always rapidly fatal. Whereas the first type seems to be associated with occlusion of only part of the hepatic veins, the very acute type can be explained by either a sudden and complete obstruction of all the hepatic veins, or more often by obstruction of the hepatic veins which had remained patent after a prior episode of partial obstruction. The clinical and biological character of the acute type has been described most frequently,[7,9] but intermediary types are also possible and many published observations do not insist on such a differentiation. This report describes two observations of the acute form. One of the authors (J.-N. M.) has seen a third case recently[5] which is quite comparable to the two cases presented here.

Case Reports

Case 1

A 40-year-old woman had an unremarkable medical history. Her disease began very suddenly with violent pain in the right and mid-epigastrium. On the evening of the same day the attending physician found an impressive hepatomegaly. The patient vomited several times, but her state did not seem to be critical. Laboratory tests were initiated, the results of which were not known until three days later (blood urea 162 mg%; total cholesterol 88 mg%; RBC 6,350,000; WBC 19,800; hemoglobin 140%; coagulation time according to Quick 23%; sedimentation rate 1 mm in one hour and 2 mm in 2 hours). The patient was then admitted to the hospital at Vierzon,† where she arrived in an obtunded state. Icterus, arterial hypotension and, above all, severe oliguria (about 100 ml/day, which was the reason for Mrs. V's transfer to the Nephrology Service of Professor G. Richet at the Hôpital Tenon) were noted. On her arrival, the patient was in a coma. The icterus had become deep, and abdominal distention with marked abdominal and presternal venous collaterals had appeared. The liver edge was evident 25 cm below the costal border in the mammary line, and the edge of the spleen was 6 cm below the left costal arch.

Paracentesis confirmed the clinical suspicion of ascites; the fluid contained 1.9 gm of protein/100 ml. The intrasplenic pressure was 30 cm of water. The diagnosis of Budd-Chiari syndrome was made, and a peritoneal dialysis was undertaken because of renal insufficiency. The pertinent results of laboratory tests can be seen in Table 1. An encephalogram shows the picture of a second-stage hepatic encephalopathy. Laparoscopy showed hypertrophy of the right lobe of the liver; the surface was pale and smooth and the anterior edge was rounded. The left lobe was atrophic, smooth and almost white. The round ligament looked somewhat hypervascular.

A liver biopsy showed a surprising amount of necrosis; almost all of the liver cells had been destroyed except for a small rim of viable periportal cells. There was no fibrosis. The hepatic veins which were visible on the slide were patent. There were no dilations of the sinusoids, but generalized hepatic infiltration existed. The entire picture was that of a pure central and mid-lobular ischemic necrosis. Angiography[6,8] between two balloons in the inferior vena cava failed to fill the hepatic veins.

After seven days of hospitalization at the Hôpital Tenon, during which time the patient remained comatose and anuric, a surgical recanalization of the hepatic vein was attempted.

Case 2

A man of 42 years had no pertinent previous medical history. On May 8, 1967, he became aware of vague abdominal pain. On May 15, he experienced a dramatic aggravation of this pain, most severe in the right and mid-epigastrium, intestinal obstruction, vomiting, and a sudden increase of the abdominal girth. RBCs were 6,500,000, WBCs 12,000.

On May 17, 1967, between 4 and 5 liters of ascites were evacuated during a laparotomy. The liver was enormous, and smooth, dirty-brown and violaceous in color. The spleen was enlarged. The portal vein had thick walls but did not seem to be thrombosed. After a liver biopsy the patient was transferred to the Hôpital Beaujon, where he arrived on the same day, awake and in reasonably good general state but jaundiced. The liver edge was 25

*See page 150.
†Hôpital Saint-Antoine Colloquium of 10-2-1968.

cm below the costal margin in the mammary line. No collateral abdominal circulation, no edema, and no spider nevi were seen. The venous pressure in the arm was 9 cm of water and did not increase upon compression of the liver. There was no evidence of proteinuria. The hematocrit was 64%, blood urea 125 mg%, and urine urea 150 mg%. His daily urine volume output was unknown. Other pertinent laboratory results are seen in Table 1.

Liver biopsy confirmed the clinical diagnosis of Budd-Chiari syndrome. There was a considerable central lobular necrosis involving about one third of each lobule. All the central lobular veins in this tissue section were thrombosed. Angiography of the hepatic veins showed complete absence of reflux. Therapeutic trial with fibrinolysins appeared to be contraindicated because of the recent laparotomy and liver biopsy. Therefore heparin therapy was undertaken and surgical relief of the venous obstruction attempted. As in the first observation, details of the surgical intervention and the postoperative courses will be reported elsewhere.

Comment

Clinical Aspects

There are many similarities in these two cases. Both patients were young and in both the onset was very acute, demanding urgent surgical intervention. This type of Budd-Chiari syndrome is rare. In the most important and extensive series published by Parker[9] it is found only six times in 149 collected cases, to which Parker added 15 of his own. The clinical symptoms in these cases appear stereotyped for those most commonly described, but there are only two cases with vomiting, abdominal pain, hepatomegaly and ascites. Only one had collateral venous circulation which was most prominent in the presternal region. Splenomegaly was found in both of our patients. According to Sherlock[10] it appears only in subacute forms, and it is possible that in the two observations which are recorded here, the splenomegaly was due as much to the polycythemia as to portal hypertension. Table 2 shows the principal clinical signs in the course of the Budd-Chiari syndrome as reported by Parker.[9]

TABLE 2

Frequency of principal clinical signs in the course of Budd- Chiari syndrome, according to Parker[9]

Ascites	93%
Hepatomegaly	70%
Venous collaterals	55%
Abdominal pain	54%
Splenomegaly	30%

Other symptoms of the Budd-Chiari syndrome are usually not mentioned at all or very seldom. The two patients of this report as well as the one who was seen more recently[5] had a deep icterus. This aspect is supposed to be very rare;[9] Sherlock denies that it happens at all.[10] At least the first of our two patients had a prolonged cardiovascular shock. This is

TABLE 1

Pertinent Laboratory Findings

	Initial Laboratory Findings		Laboratory two to six days later	
	Case J.V.	Case M.R.	Case J.V.	Case M.R.
Total bilirubin (mg/100 ml)	13.0	11.7	11.0	14.5
Unconjug. bilirubin (mg/100 ml)	3.2	3.7	3.0	4.5
Alkaline phosphatase (in Bessey units—normal <2U)	5.75	2.50	1.20	4.0
Cholesterol E/T (g/100 ml)	0.01/0.052	0.044/0.066	0.030/0.048	0.046/0.1
SGPT	3,600	4,600	85.	500
SGOT	1,700	3,600	155	1,350
Total protein (g/100 ml)	5.8	5.6	4.8	7.0
Ser. albumin (g/100 ml)	3.2	3.8	2.9	4.7
Quick (p. 100)	21	32	37	26
Fibrin.	—	2.60	—	—
Platelets/μL	103,000	280,000	—	225,000
Blood urea	1.80	1.40	2.10	1.95
Urine urea mg/100 ml	1.00	1.10	.40	.70
Hematocrit (p. 100)	61	64	37	38
Ascites-total proteins (g/100 ml)	1.9	4.8	—	—

only rarely reported,[7,9] but undoubtedly it resembles the shock which one can see after experimental ligature of the inferior vena cava. It is possible that a sudden obstruction of the hepatic vein is followed by pooling of blood in the splanchnic area, accounting for at least part of the shock. The renal shutdown observed in both cases cannot be attributed unreservedly to shock, and the post-mortem histologic findings in the kidneys were unable to explain it. Renal insufficiency has been observed rather often,[7] though it does not enter into the discussion of Parker.[9]

Biological Aspects

Among the laboratory findings, a *decrease of serum cholesterol* is generally found.[1,7,11] It was present in both of our patients. The *total protein* content of the ascitic fluid in the Budd-Chiari syndrome is still the object of discussion; as early as 1956 Caroli[1] noted that the proteins of the ascites are more often on the low side.[7] The first of our patients had only 1.9 gm of proteins per 100 ml of ascites. It is certain that the protein content of the ascites due to a pure Budd-Chiari syndrome, involving only the hepatic veins, is quite variable and often very little elevated. If, however, the inferior vena cava is involved in the obstructive process, we find a rise of the ascitic protein content. These differences do not seem to be appreciated in the principal reports, and often one finds an insistence that the Budd-Chiari syndrome is always associated with a definite rise in total ascitic protein.

The *bilirubinemia* of these two cases was remarkable and surpassed even the maximum value of Parker's series[9] which is 13.4 mg/100 ml. It is quite possible that our patients survived through a longer period of time than was possible several years ago, thus affording a greater time span for the development of a deeper icterus. Indeed, in both of our patients the icterus had been quite mild during the first week of illness, and became very severe only immediately prior to death.

In both cases the *transaminase values reached extremely high levels* similar to those observed in toxic or viral hepatitis, an increase corresponding well with the magnitude of necrosis on the histologic sections. However, one can make the following statements: (1) the authors have not found any mention of hypertransaminasemia in the literature; (2) hypertransaminasemia appears to be short-lived and may therefore be missed.

The laparoscopy of the first observation failed to show the "dirty brown color" which has been described by Caroli.[2] This sign was found only in our second patient. At laparoscopy the great intensity of the necrosis together with a white-appearing liver may explain that in very acute cases or those which are seen late, the *ischemic necrosis* can predominate over stasis. It should also be mentioned that neither one of these two patients showed hypertrophy of the lobe of Spigel which is often found in the Budd-Chiari syndrome and which implies the patency of the spigelian veins which empty directly into the inferior vena cava. The lobe of Spigel could thus serve as efferent drainage for an area of the liver, the hepatic veins of which are obstructed. As far as the asymmetry of the liver is concerned it corresponds to two successive obstructions of the hepatic veins. This seems to be almost the rule in the course of the Budd-Chiari syndrome[3,9]; the first episode in such cases can be subclinical.

In these two patients as well as in the third patient seen by one of the authors[5] it is very likely that the *obstruction of the hepatic veins occurred secondary to a polycythemia* which had been clinically latent until that time. This may be assumed for the following reasons: (1) at no time could the polycythemia be explained by hemoconcentration; (2) in all of these cases immature red and white blood cells were found in the peripheral blood; and (3) several bone marrow biopsies done at autopsy suggest the Vaquez syndrome. If polycythemia was actually present at the beginning of our observation, it would appear that it progressively disappears as the Budd-Chiari syndrome persists and is aggravated, and thus may not be recognized. In the large series of Budd-Chiari syndromes published by Parker, one finds an etiology of this syndrome in only 30% of the cases, and a third of those (10% of the total cases of Budd-Chiari syndrome) had a polycythemia at the beginning of the syndrome. In a more recently reported series,[3] three of six cases of Budd-Chiari syndrome are explained by the Vaquez syndrome.

The connection of this syndrome with throm-

bosis of the hepatic veins was the object of a recent well documented work by Clauvel et al.,[4] wherein it is noted that in the large series which have been published on Vaquez disease (polycythemia vera) thrombosis of hepatic veins is found in 25% of the cases, although 30-40% showed thromboses elsewhere. Another facet has to be considered: Whereas the Vaquez syndrome occurs most commonly towards the age of 55 years, the patients with Budd-Chiari syndrome and polycythemia are much younger: 39 years on the average. There is no explanation for this discrepancy which certainly would prove embarrassing whenever one postulates that the polycythemia might be the etiologic factor of the Budd-Chiari syndrome in relatively young subjects as they are reported here.

Summary

Two cases of Budd-Chiari syndrome, both associated with polycythemia have been observed. Their typical clinical symptoms and the low cholesterol values make the diagnosis easy. The ascitic protein level is variable. Unlike most of the other published cases, deep jaundice and renal insufficiency were present in both patients. The authors stress two points: (1) very high, but very rapidly decreasing serum transaminases and (2) possible ischemic necrosis seen on liver biopsy, with a pale-appearing liver at laparoscopy. These cases evolved rapidly towards portacaval encephalopathy, and the necessity of emergency treatment is emphasized.

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No Boundaries in Medicine

Medicine gives us a vision of what the world could be: it embodies the hope of the great community, in which man unites to master nature and harness its laws to the service of the entire human race. For there is no Jewish or Aryan medicine, there is no German, Italian, or British physiology, there is no color line in endocrinology, no class war in chemotherapy. In the roster of medical discovery, it is difficult to find a great contribution that was made by one man working alone, or even by the scientists of one nation depending on their own unaided researches. Everywhere science works on a communal basis; the findings of one worker are freely published for the information of all, and each discovery is but a capstone placed on the previous contributions of scores and hundreds of other workers representing many nations and many races.*

*George W. Gray: The Advancing Front of Medicine, 1941.

The Application of Computer Techniques to the Laboratory Diagnosis

Diseases of the Liver and Biliary System

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THE USE OF COMPUTERS has already resulted in numerous applications in medicine: automated medical history, processing of laboratory data, assisted training and aid in medical diagnosis.

Although no theoretical or practical difficulties should prevent the accomplishment of medical diagnosis by computer, it has not been adopted in general medical use. Nevertheless, considering the speed with which new knowledge and techniques become available, the physician is confronted with ever increasing amounts of information, and is in danger of utilizing them only incompletely and imperfectly.

Several experiments have already demonstrated the efficiency of computers in medical diagnosis, particularly in cardiology and endocrinology.[6,7,13,15]

This study presents a program which appears to be helpful in the diagnosis of liver diseases. Established for 35 diseases of the liver and biliary tract, it employs exclusively laboratory findings; no clinical signs are taken into account. Its performance has been tested in diseases with firmly established diagnoses, and has been compared with the diagnoses of two specialists in liver diseases and two in internal medicine.

Material and Methods

Eleven biological parameters were used; they were derived from the eight most commonly used liver function tests: serum glutamic pyruvic transaminase (S.G.P.T.), alkaline phosphatase, prothrombin time, total cholesterol, serum protein electrophoresis (albumin, alpha$_2$-globulins, gamma-globulins), the Maclagan test, serum bilirubin (total and unconjugated), bromsulphalein (BSP) test (Table 1).

TABLE 1
Laboratory Tests Used in the Program

Serum glutamic-pyruvic transaminases (S.G.P.T.)	
Alkaline phosphatase	
Prothrombin time	
Total serum cholesterol	
Serum electrophoresis	• albumin • alpha 2-globulins • gamma-globulins
Maclagan test	
Bilirubin	• total • unconjugated
Bromsulphalein test	

For each biochemical analysis including these 11 parameters, the aim of the program was to assign a probability to each of the diseases and thus to furnish a diagnostic orientation. The differential diagnosis encompassed 35 hepato-biliary diseases (or syndromes), which are enumerated in Table 2.

Bayes' theorem[1] was used for the calculation of the probability:

$$P''(Mi/Z) = \frac{P'(Mi) \times P(Z/Mi)}{\sum_{k=1}^{35} P'(Mk) \times P(Z/Mk)}$$

P″ (Mi/Z) is the probability to be determined: the probability P″ of having the disease Mi for the biological pattern, Z, also the "a posteriori" probability. This probability depends on two factors: (a) on the one hand, on the frequency of the disease within the liver diseases; it is P′ (Mi), the "a priori" probability; (b) on the other hand, on the biological pattern, P (Z/Mi), the probability of observing the biological pattern Z in the disease Mi; this is the likelihood function. The denominator of the fraction represents the sum of the products from the numerator of the 35 fractions.

The "a priori" probabilities, P′ (Mi), were evaluated from about 1,000 medical records of a hepatology medical department. The likelihood function values, P (Z/Mi), were obtained by calculation for each tested biological pattern. However, such a calculation is possible only if

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the probability distribution of the laboratory parameters have been previously determinated for all the diseases. A concrete example of probability distribution is that of S.G.P.T. during the first week of viral hepatitis; the value exceeds 500 U pyruvic acid units in 75% of the cases; it is never below 150 U (Figure 1).

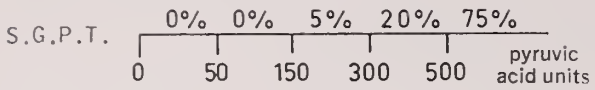


Fig. 1—Example of the distribution of the probabilities involving S.G.P.T. in the first week of viral hepatitis.

The distribution of the probabilities of the 11 biological parameters were based on published statistical data as well as on personal medical records.

The calculation of the likelihood function assumes that the parameters used are mutually independent;[1,8] however, it has been shown that several of these parameters do have a correlation. In order to satisfy the required independence, several of them have been grouped according to the schema proposed by Fauvert:[5] (1) prothrombin time, total serum cholesterol and serum albumin as a function of hepatocellular failure, (2) the Maclagan test and gamma-globulins as a function of inflammation. Thus, the 11 parameters were reduced to eight independent variables: Z1, Z2 . . . Z8.

For any biological pattern Z, the probability P (Z/Mi) equals the product of the probabilities of these eight variables.[21,22-28]

$$P(Z/Mi) = P(z1/Mi) \times P(z2/Mi) \ldots P(z8/Mi)$$

A single abnormal laboratory value does not imply necessarily the existence of a disease of the liver or biliary system. For instance, an increase in alkaline phosphatase can be observed in a bone disease or an increase in gamma-globulins, in a dysproteinemia. These events have been taken into account in the program.

The program was written in FORTRAN IV, compiled and executed on the 90-80 C.I.I. system of the I.R.I.A. computer center.

Results

The performance of the program has been tested with a sample of 51 diseases with known diagnoses; this sample was not used to establish the probability distributions. The results are shown in Figure 2.

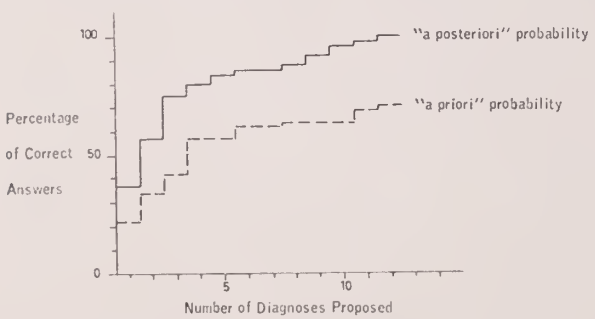


Fig. 2—Percentage of correct answers as function of the diagnoses given by the computer as the most likely. The "a priori" probabilities consider only the incidence of the disease. The "a posteriori" probabilities give account of incidence as well as of the laboratory pattern of the disease.

For the "a posteriori" probability as well as the "a priori" probability, the percentage of correct answers could be expressed graphically as a function of the number of diagnoses proposed by the computer system.

The difference between the two lines expressed the usefulness of laboratory tests in diagnosis. The solid line (based on the "a posteriori" probabilities) indicated that the percentage of correct answers was 80%, if one considered the four diagnoses which were given by the computer as the most likely.

The performance of the program was also tested with the same sample group of diseases.

TABLE 2

Number	Disease	Probability (%)
1	Secondary liver cancer	85.09989
2	Liver abscess	6.47893
3	Hemochromatosis	3.27996
4	Amyloidosis of the liver	1.82370
5	Hepatic Hodgkin's disease	1.11357
6	Liver flukes without jaundice	0.58023
7	Anicteric cholestasis, benign or malignant	0.58023
8	Alcoholic cirrhosis	0.34692
9	Hepatic granulomata	0.34194
10	Primary liver cancer with cirrhosis	0.15065
11	Congestive heart failure—liver	0.09086
12	Primary biliary cirrhosis	0.03736
13	Hydatid disease	0.02516
14	Alcoholic fatty liver	0.02368
15	Viral hepatitis in the 3rd or 4th week	0.02076
16	Congenital hepatic fibrosis	0.00234
17	Post-hepatic cirrhosis	0.00199
18	Alcoholic fatty liver with cholestasis	0.00061
19	Chronic hepatitis	0.00038
20	Hepatic schistosomiasis	0.00031
21	Infectious mononucleosis	0.00029
22	Benign liver tumors	0.00024
23	Viral hepatitis in the 1st or 2nd week	0.00000
24	Pre-icteric stage of hepatitis	0.00000
25	Fulminant hepatitis	0.00000
26	Jaundice due to malignant obstruction	0.00000
27	Jaundice due to gall-stones	0.00000
28	Hemolytic jaundice	0.00000
29	Gilbert's disease	0.00000
30	Cholestatic drug hepatitis	0.00000
31	Cytolytic drug hepatitis	0.00000
32	Mixed drug hepatitis	0.00000
33	Toxic hepatitis	0.00000
34	Prolonged viral hepatitis	0 00000
35	Liver flukes with jaundice	0.00000

Example of correct answer given by the computer: The disease tested is a secondary liver cancer. The laboratory tests are: SGPT: 45 pyruvic acid units, alkaline phosphatase: 19 King-Armstrong units, prothrombin time: 80%, total cholesterol: 0.23 g/100 ml, serum albumin: 2.6 g/100 ml, alpha$_2$-globulins: 1.6 g/100 ml, gamma-globulins: 1.2 g/100 ml, Maclagan test: 11 Vernes units, total serum bilirubin: 0.4 mg/100 ml, BSP test: abnormal. A probability is assigned to each of the 35 diseases, which are shown in decreasing order of probability.

but without the 11 cases of alcoholic cirrhosis. Theoretically these cases of cirrhosis could have weighted favorably on the "a priori" probabilities and improved the program performances. However, the "a posteriori" probabilities established on this reduced sample were similar to those of the complete group (Figure 3).

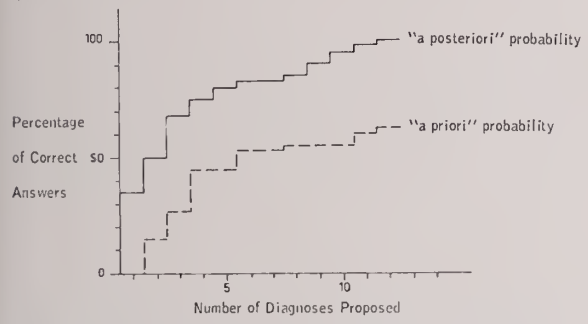


Fig. 3—Percentage of correct answers as function of the number of the most probable diagnoses according to the computer, exclusive of alcoholic cirrhosis.

The diagnoses furnished by the computer for a sample of 30 patients were compared to those of two specialists in liver diseases and two in internal medicine. The performances of the two hepatologists were nearly identical and neither was significantly different ($P > 0.05$) from those of the computer (Table 3 and Figure 4). The diagnoses of the two internists were also nearly identical, but both were significantly inferior ($P < 0.05$) to those of the computer (Table 4, Figure 5).

Discussion

Theoretically there is no reason why the computer cannot be put to practical use in research as well as in clinical problems. However, it seems that these methods have not been incorporated into the clinical routine. What are the reasons? First of all, this diagnostic aid might not fill a real need, or the existing computer programs might not be adequate. However, on the one hand, the difficulties which face the physician daily should remind us that such a need exists; on the other hand, the experiences which have been gathered already in such diverse fields as the diagnosis of congenital cardiopathies,[15] diseases of the thyroid gland,[6,13] bone diseases,[9] and the automatic interpretation of electrocardiograms,[7] are impressive.

The reasons for this slow popularization find their explanation in methodology as well

TABLE 3

Comparison of the Answers of the Computer with Those of the Two Hepatologists, Considering the Five Most Likely Diagnoses

	Number of cases tested	Number of correct answers	
Computer	30		25
			P>0.05
Hepatologist I	30	P>0.05	21
Hepatologist II	30		24

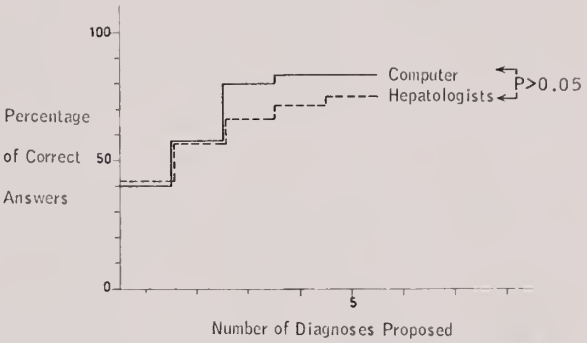


Fig. 4—Comparison of the answers of the computer and two hepatologists. The answers of the two physicians are nearly the same; the curve represents the mean of the two answers.

TABLE 4

Comparison of the Answers of the Computer with Those of the Two Internists, Considering the Five Most Likely Diagnoses

	Number of cases tested	Number of correct answers	
Computer	30		25
			P<0.05
Internist I	30	P<0.05	16
Internist II	30		17

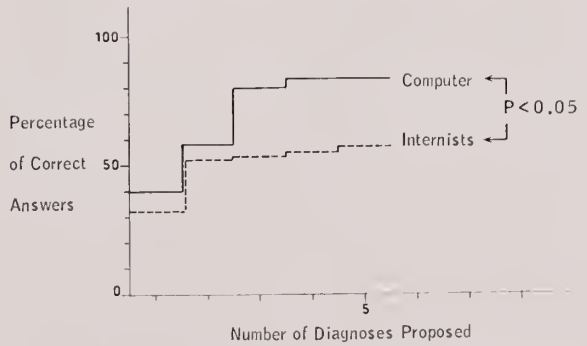


Fig. 5—Comparison of the answers of the computer and two internists. The answers of the two physicians are nearly the same; the curve represents the mean of the two answers.

as in technology: at times, it is difficult to formulate the lines of the physician's reasoning; the statistical information concerning diseases and their symptoms are often insufficient; the limited amount of available automatic equipment and the difficulties which still exist in the communication with the computer have the effect that the physician is not familiar with modern methods relating to computer data processing.

From a practical viewpoint, hepatology lends itself easily to the diagnostic use of the computer. As a matter of fact, it represents a limited field of pathology where the differential diagnosis involves only a relatively small number of diseases.

The Diagnosis of Jaundice

Several experiments have already been undertaken to aid diagnosis in this specialty.[3,4,10,11,12,14] The aim of most of them was the differential diagnoses between intra- and extrahepatic jaundice.

The study of Burbank[3] in particular dealt with six causes of jaundice and was based on 70 clinical, laboratory, radiological and histological parameters. Bayes' theorem was used for calculations. The computer diagnosis was correct in 77% of the cases in 52 diseases; the indications of laparotomy seemed justified in 98%.

In the present study, the differential diagnosis is based only on 11 biological parameters and is applied to a much greater number of hepato-biliary diseases; this may explain the reason why the diagnosis of the strongest probability is correct in only 37%; but when one considers the four most likely diagnoses, then the correct diagnosis can be found among them in 80% of the cases.

Two points deserve further consideration: the methods of calculation and the performance of the program.

The Method of Calculation

Bayes' models have frequently been employed in problems of medical diagnosis. Their use is indicated especially if, as in the present case, the signs have poor discriminatory quality if they are taken separately, if it is possible to assign a distribution of probability to them for each disease, and if one can evaluate the frequency of these diseases. The use of Bayes' theorem presupposes that the results of the laboratory tests used are independent of one another[1,8]; for this reason, some laboratory results have been grouped according to function. In fact, it seems that Bayes' formula can be used efficiently in situations where the conditions of independence have not been strictly observed.[3] It is interesting to note that there is a certain analogy between Bayes' procedure of calculation and the way a physician reasons. In order to make his diagnosis, the physician keeps the relative incidence of disease in mind, as well as the characteristics of the laboratory pattern: two factors also encountered in Bayes' theorem.

The Program's Performance

The diagnostic aid programs which have been designed in the field of hepatology thus far had the goal of distinguishing medical from surgical jaundice. The present study has extended the differential diagnostic field to nearly all the diseases of the liver and biliary tract. Although the 35 diseases studied cover the greatest part of hepatology, certain rare diseases have not yet been taken into account, such as the Budd-Chiari syndrome or Wilson's disease.

It is conceivable that the performance of the present program can be improved by: (a) a better knowledge of the distribution of the probabilities involving the laboratory tests, by means of the accumulation of medical records; (b) the introduction of supplementary informations on these diseases, particularly the clinical signs; (c) an intensified inquiry into the respective frequency of the diseases. However, the epidemiologic data are difficult to know with accuracy, and they do vary depending on hospital departments.

Computer vs Physician

The comparison of the computer performances and those of the physicians indicates that the computer's results are similar to those of the two hepatologists, but superior to the diagnoses of the two internists.

It is interesting to note (Figure 5) that the difference between the computer and the two internists is significant when one considers the five most probable diagnoses, but it is not significant if one takes only the first two diagnostic possibilities into account. This fact demon-

strates concretely that the computer as well as the physicians are able to recognize the disease with a high incidence and/or a characteristic laboratory pattern in the same proportion of accuracy, but that the computer recognizes, with greater ease, rare diseases and/or diseases with a non-typical laboratory pattern.

The comparison between the performance of computer and physician may appear artificial, considering that the latter utilizes clinical observations. This comparison, however, points out an important element: time. In this experiment, where each individual physician needed about three hours to make his diagnoses for the 30 cases tested, the computer gave its answer in a few minutes. In practice, the physician is often only partially able to utilize all the available information; but it is realistic to think that in the near future the clinical laboratories will return their results with commentaries which will be helpful to the physician in his diagnosis. The clinical laboratories, however, will have to make an effort to standardize their laboratory techniques, and to express the results in the same units.

Summary

A program for computer-aided diagnosis of diseases of the liver and biliary system is presented. Thirty-five such diseases were considered. The program was based solely on the eight most commonly used laboratory liver-function tests, and no clinical signs were taken into account. The aim of the program, for each biochemical analysis comprising the eight tests, was to assign a probability to each of the 35 diseases and thus to predict the likely diagnosis. The probabilities were calculated according to Bayes' theorem.

The performances of the program were tested on a sample of 51 cases with established diagnoses: in 57% of these the correct diagnosis was one of those estimated by the computer as the two most probable, and in 80% it was among those estimated by the computer as the four most probable. The computer diagnoses were compared with those made by two specialists in diseases of the liver and two in internal medicine respectively: the computer made the same number of correct diagnoses as the liver specialists; between computer and internists there was a significant difference in favor of the computer.

Acknowledgements

The authors thank Drs. M.-J. Grange, P. Berthelot, Y. Hecht, J. Marsac and S. Erlinger for their friendly cooperation.

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Epigram

What fools indeed we mortals are
To lavish care upon a Car,
With ne'er a bit of time to see
About our own machinery.
—John Kendrick Bangs

Historic Hospitals

Hôtel Dieu, Paris



Hôtel Dieu, Paris. Courtesy of National Library of Medicine, Bethesda, Maryland.

One of the world's oldest hospitals is the Hôtel Dieu of Paris. It stands near the Cathedral of Notre Dame on the island in the Seine where the city began, the Ile de la Cité. The model of many other French hospitals, the Hôtel Dieu was founded in 660 A.D. by St. Landry, the twenty-eighth bishop of Paris. Until the seventeenth century, it was the city's sole public hospital.

In the early Middle Ages, the hospital was mainly a locale for the practice of Christian charity. The spiritual welfare of the patients, patrons, and hospital personnel was considered of prime importance, while physical conditions and nursing care remained primitive. Under the rule of St. Augustine, the women of the Hôtel Dieu maintained both a religious community and the beginning of a nursing order. In the woodcut reproduced here and entitled "Reception of a Novice," a young girl is being welcomed into the community, while at another door a litter-borne patient is being admitted for care.

Physicians, if present at all, occupied a relatively unimportant place. It is recorded, however, that as early as 1221 there was engaged a surgeon to treat the sick and poor at Hôtel Dieu. The most famous surgeon associated with the hospital was Ambroise Paré, who was compagnon chirurgien, a sort of surgical resident, for three years during the 1530s. In his later writings, Paré referred with pleasure and pride to the invaluable experience which he gained there.

In its long history the Hôtel Dieu has undergone innumerable changes, enjoyed periods of excellence and suffered from neglect and mismanagment. One notable rehabilitation was accomplished by the celebrated St. Vincent de Paul, founder of the Society of the Sisters of Charity in the seventeenth century. Additional reforms were made at the time of the French Revolution.

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Minneapolis, Minnesota

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Maximal Biliary Transport of Sulfobromophthalein in the Wistar Rat

A Critical Study *

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DYE EXCRETION by the liver, as in the case of bilirubin and bile salts, involves three steps: (1) uptake by the hepatic cell, (2) intracellular transfer, with possible conjugation, and (3) excretion into bile. It is generally accepted that this latter process is limited by a maximal rate of excretion.[7] However, several authors recently demonstrated that the maximal transport of sulfobromophthalein (BSP) or bilirubin was not a constant parameter, but could be increased during choleresis produced by bile salt infusions.[5,6,16,17,22,23] The aim of this work is: (1) to show that large infusion rates of BSP in the rat markedly reduce both bile flow and maximal transport of BSP (BSP Tm); another criticism of the concept of BSP Tm in this animal is therefore presented; (2) to define the relationship between bile flow and biliary maximal excretion.

Methods

Experimental Procedure

All the experiments were performed on male Wistar CF rats,† weighing 155-300 g. The animals were anaesthetised with mebubarbital‡ (4.5 mg/100 g b.w., i.p.); rectal temperature was monitored at 38° ± 0.5°C. Tracheotomy was performed. The bile duct was cannulated and bile collected in weighed tubes at 10-min intervals. For the infusions, BSP§ (mol. wt: 838) was diluted with 0.15 M NaCl. The infused solution was kept at pH8 with mebubarbital used for maintainance of the anaesthesia. BSP administration, started after a 50- to 60-minute control period of bile flow during this period, a 0.15 M NaCl infusion (50 μl/min/rat) was given. BSP infusion rates ranged from 235 to 350 μg/min/100 g b.w. (280 to 418 nmoles/min/100 g b.w.), in a volume of 50 μl/min/rat. Prior to the beginning of BSP infusion, a priming dose of 4 mg (4.8 μmoles)/100 g b.w. had been given. These BSP infusion rates were well in excess of the expected Tm; in each experiment, four or five blood samples were collected, and plasma BSP concentrations were continuously rising. Thereafter, infusion rates exceeding the maximal excretion rate will be called "supramaximal."

BSP infusion experiments were performed on 41 rats. In 28 animals, BSP was infused during 60 minutes. In 10, it was given during 150 minutes; five of these (Group I) received from 240 to 270 μg/min/100 g b.w. and five others (Group II), from 295 to 325 μg/min/100 g b.w. In three rats, sodium dehydrocholate was administered intravenously after 100 minutes of BSP infusion. Sodium dehydrocholate# (mol. wt: 447) was diluted with 0.15 M NaCl and was infused at the rate of 200 μg/min/100 g b.w. (448 nmoles/min/100 g b.w.) for 60 minutes, in a volume of 50 μl/min/rat; a priming dose of 2 mg (4.5 μmoles)/100 g b.w. was given intravenously prior to the start of the infusion.

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†Provided by C.N.R.S., F 91-Gif-sur-Yvette.
‡Abbott, F 93-Montreuil-sous-Bois.
§Serb, F 75-Paris.
#Théraplix, F 75-Paris.

TABLE I
Bile Flow during BSP Infusions of "Supramaximal" Rates in Wistar Rats
(mean values ±1 SD)

BSP infusion rates (μg/min/100 g b.w.)	Initial bile flow (mg/min/100 b.w.)	Bile flow during BSP infusion (mg/min/100 g b.w.) 10-30 min	40-60 min	80-100 min	130-150 min
240-270 (5 rats)	9.7 ±3.3	9.0 ±2.6	8.3 ±3.2	7.1 ±3.1	4.9 ±2.4
295-325 (5 rats)	8.1 ±2.9	8.2 ±2.2	7.3 ±2.3	5.1 ±1.7	2.1 ±0.8

Analytical Methods

Bile and plasma concentrations of BSP were determined on a PM Q II Zeiss spectrophotometer at 580 nm, after appropriate dilution with 0.05 N NaOH.

The percentage of BSP conjugates in bile was measured in five rats. Conjugates were separated by descending paper (n°1 Whatman) chromatography; the solvent system was n-propanol : acetic acid : water (10:1:5 v/v). BSP conjugates were detected by spraying with a 20% w/v solution of Na2 CO3 and eluted together in 0.05 N NaOH.

Bile salt concentrations in bile were determined by an enzymatic method derived from Talalay[26] and already used by Javitt and Emerman[19]; very few modifications were introduced which will be reported in detail elsewhere.[3]

Statistical analysis of the results was performed according to the usual methods.[21,24]

Results

Effects of BSP Infused at "Supramaximal" Rates on Bile Flow, BSP Biliary Excretion and BSP Conjugation

In these experiments, BSP progressively decreased the bile flow when infused at rates exceeding the maximal biliary excretion rate. A typical experiment is shown in Figure 1. The fall in bile flow became statistically significant only when the infusion had been given for at least 90 minutes. Bile flow measured in the 130 to 150-min infusion period was compared to bile flow obtained during the control period. In the animals receiving 240-270 μg/min/100 g b.w. (Group I), the decrease was 49 ± 28% (mean ± 1 SD) (Figure 2; Table 1); in the animals receiving 295-325 μg/min/100 g b.w. (Group II), the decrease was 74 ± 7% (Figure 3; Table 1); the difference was not significant ($P > 0.05$). In eight control animals, receiving NaCl infusion, no significant variation in bile flow could be observed for a 210-min period (Figure 4).

In BSP-infused animals, a progressive decrease of biliary output of BSP was observed

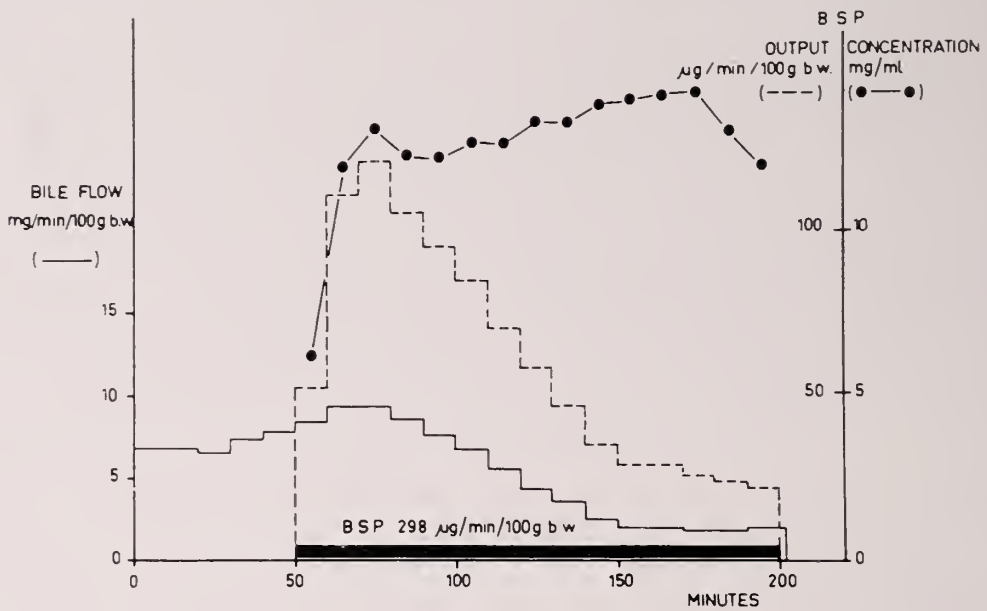
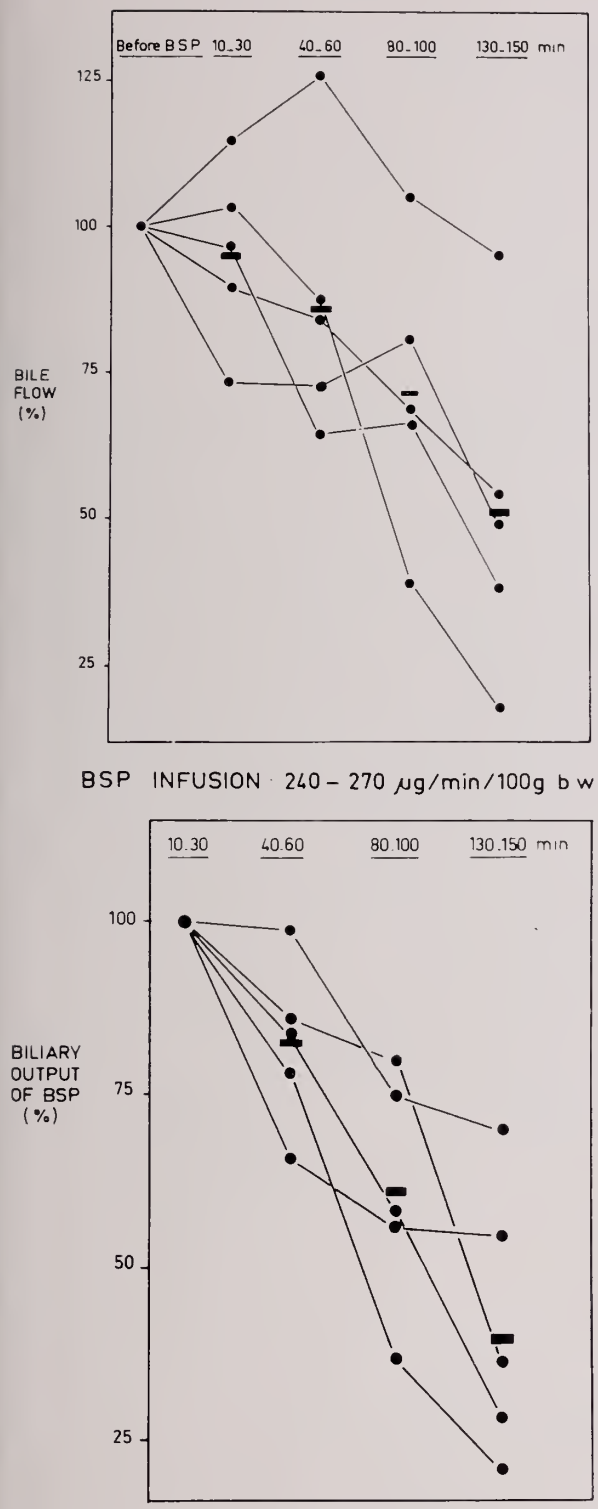


Fig. 1—Bile flow, biliary BSP concentration and BSP output in a Wistar rat receiving BSP infusion at the rate of 298 μg/min/100 g b.w.

TABLE 2

Biliary BSP Output during BSP Infusions at "Supramaximal" Rates in Wistar Rats. (mean values ±1 SD)

BSP infusion rates (μg/min/100 g b.w.)	Biliary BSP output (μg/min/100 g b.w.) 10-30 min	40-60 min	80-100 min	130-150 min
240-270 (5 rats)	130 ±43	111 ±51	83 ±41	55 ±38
295-325 (5 rats)	106 ±34	91 ±30	58 ±18	19 ±9



together with the decrease of bile flow (Figure 1). Maximal excretion rate was reached generally 10 to 30 minutes after the beginning of the infusion. BSP output measured in the 130- to 150-min infusion period was compared to that obtained in the 10- to 30-min infusion period. The decrease of BSP biliary excretion was 60 ± 19% in the Group I rats (Figure 2; Table 2) and 83 ± 3% in the Group II (Figure 3; Table 2); the difference was significant ($P < 0.05$).

In contrast, only small variations in BSP concentration in bile were observed; in Group I, BSP concentration fell by 23 ± 22% (Figure 2; Table 3) and in Group II, by 28 ± 36% (Figure 3; Table 3); the difference was not significant ($P > 0.05$).

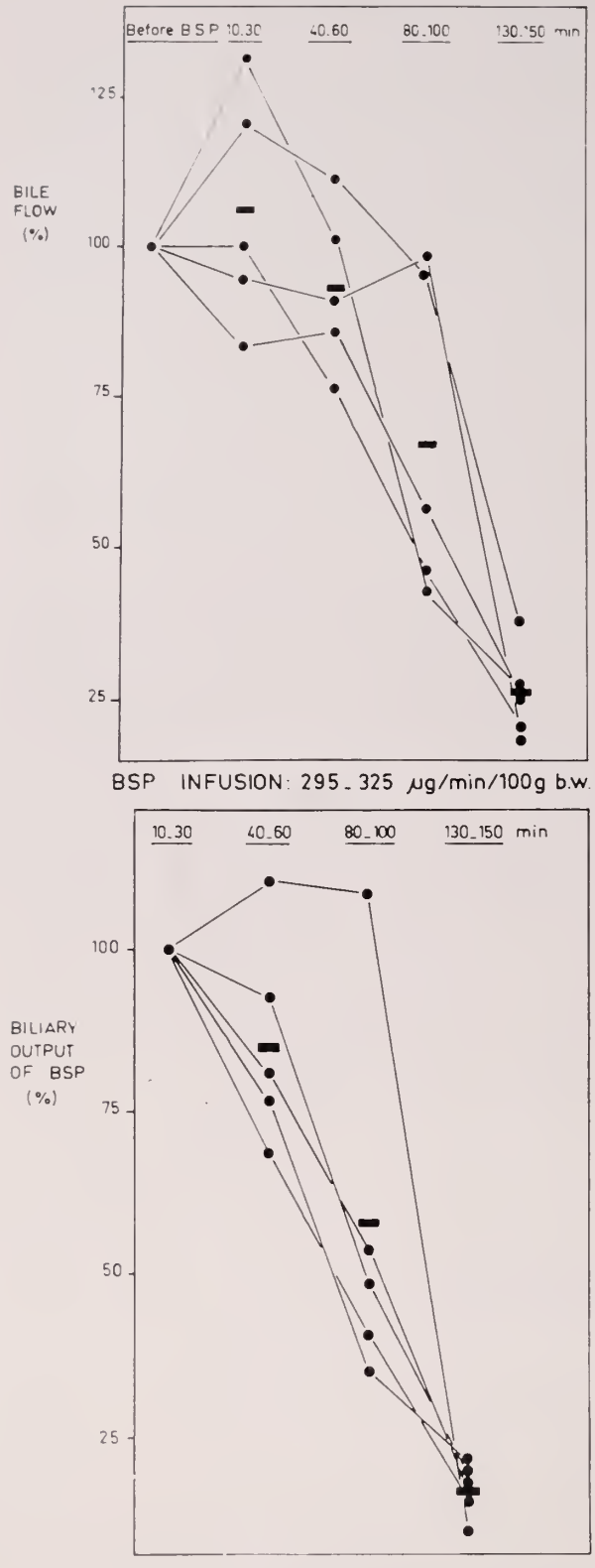
In the same experiments, the percentage of BSP conjugates in bile decreased. It was 81 ± 3% in the 20- to 30-min infusion period and 52 ± 12% in the 120- to 130-min period (Table 4); the difference was significant ($P < 0.01$).

Effects of BSP Infused at "Supramaximal" Rates on Bile Salt Excretion

In four control animals, receiving only NaCl

Fig. 2—Bile flow (top), biliary BSP output (bottom-left) and biliary BSP concentration (right) in five Wistar rats being given a BSP infusion at the rate of 240 to 270 µg/min/100 g b.w. In each period, the dark bar (—) represents the mean value.

Top: 100% represents the bile flow for the initial 50- or 60-min period. Bottom-left: 100% represents the biliary BSP excretion rate for the 10- to 30-min period after the start of infusion. Bottom-right: 100% represents the biliary BSP concentration for the 10- to 30-min period after the start of infusion.



infusion, bile salt output in bile measured during the 0 to 30-min period and the 180 to 210-min period, fell by 58.0 ± 11.0% (Table 5). In four other animals, after 60 minutes, NaCl infusion was replaced by BSP infusion (282 to 325 µg/min/100 g b.w.). In this latter group, bile salt output in bile fell by 80.8 ± 12.8% (Table 5). The difference was significant ($P < 0.05$).

Effects of Sodium Dehydrocholate on BSP Tm

Sodium dehydrocholate infusion increased both bile flow and BSP excretion in bile. In three rats, the 20-min period before sodium dehydrocholate administration and the 20- to 40-min period after the beginning of infusion were compared. The increase in bile flow was on the average 62% and that in BSP output was 22%. A small decrease of BSP concentration in bile was observed (Table 6); this decrease was not significantly different from that found in animals receiving no dehydrocholate ($P > 0.05$).

Relationship between Maximal Excretion Rate of BSP and Initial Bile Flow

In 41 rats, BSP Tm measured in bile of the

Fig. 3—Bile flow (top), biliary BSP output (bottom-left) and biliary BSP concentration (right) in five Wistar rats being given BSP infusion at the rate of 295 to 325 µg/min/100 g b.w. In each period the dark bar (—) represents mean value.

Top: 100% represents the bile flow for the initial 50- or 60-min period. Bottom-left: 100% represents the biliary BSP excretion rate for the 10- to 30-min period after the start of infusion. Bottom-right: 100% represents the biliary BSP concentration for the 10- to 30-min period after the start of infusion.

TABLE 3

Biliary BSP Concentration during BSP Infusions at "Supramaximal" Rates in Wistar Rats (mean values ±1 SD).

BSP infusion rates (μg/min/100 g b.w.)	Biliary BSP concentration (mg/ml) 10-30 min	40-60 min	80-100 min	130-150 min
240-270 (5 rats)	14.5 ±3.1	13.2 ±3.0	12.6 ±3.1	11.5 ±3.7
295-325 (5 rats)	13.8 ±0.8	13.3 ±1.8	12.3 ±2.2	10.0 ±2.1

TABLE 4

Percentage of BSP Conjugates in Bile of Wistar Rats in the 20- to 30-min Period and the 120- to 130-min Period of BSP Infusions at "Supramaximal" Rates.

Body weight of rats (g)	Percentage of BSP conjugates in bile (%) 20-30 min	120-130 min
275	82	47
280	79	63
280	80	66
300	77	42
300	86	42
	—	—
Mean	81	52
1 SD	3	12
	$F = 24.10$	
	$P < 0.01$	

TABLE 5

Bile Flow, Bile Salt Concentration and Output in Bile of Rats. Four Control Rats Received NaCl Infusion and Four Other Rats BSP Infusion at "Supramaximal" Rates.

	NaCl infusion (4 rats) 0-30 min	180-210 min	Percentage of decrease	BSP infusion* (4 rats) 0-30 min	180-210 min	Percentage of decrease
Bile flow (mg/min/100 g b.w.)	7.33±1.58	6.39±1.48	12.3±13.3	7.27±1.42	2.28±1.42	70.4±13.3
Bile salt concentration (nmoles/ml)	18.7±5.3	8.8±2.5	52.1±12.0	22.3±2.1	15.4±8.4	31.5±34.1
Bile salt output (nmoles/min/100 g b.w.)	138.8±55.0	55.5±20.0	58.0±11.0	164.3±42.8	32.3±25.6	80.8±12.8

*In this group of rats, BSP infusion replaced NaCl infusion after 60 minutes.

TABLE 6

Effect of Sodium Dehydrocholate Infusion (448 nmoles/min/100 g b.w.) on BSP Tm in Wistar Rats. First Period (I) is the 20-min Period Sodium Dehydrocholate Administration; Second Period (II) is the 20- to 40-min Period after the Start of Infusion.

Body weight of rats (g)	Bile flow (mg/min/100 g b.w.) I	II	Biliary BSP output (μg/min/100 g b.w.) I	II	Biliary BSP concentration (mg/ml) I	II
190	11.1	20.4	130.5	184.9	11.7	9.0
155	7.7	11.8	64.4	81.2	8.2	6.9
290	4.3	5.2	52.8	66.1	10.9	12.6
	—	—	—	—	—	—
Mean	7.7	12.5	82.6	110.7	10.3	9.5

10- to 30-min infusion period was correlated with bile flow of the control period. There was a highly significant correlation between these two parameters ($P < 0.001$) (Figure 5).

Discussion

Under the conditions of these experiments in the Wistar rat, the so-called BSP Tm could be altered in two ways: (1) when BSP infusions exceeding the expected Tm were given, BSP Tm was not steady, but decreased progressively; (2) as in other animal species,[17,22,23] BSP Tm could be increased by choleresis produced by bile salt infusion. In both cases, BSP Tm appeared to be closely dependent on variations in bile flow.

The concept of BSP Tm has been extensively studied in the dog.[27,28] When BSP was infused in that animal three hours at "supramaximal" rates, there was no decrease of bile flow and BSP biliary output.[28] In contrast, in the Wistar rat, large infusion rates of BSP progressively decreased both bile flow and dye excretion rate in bile. The same changes were found recently by other authors using the isolated rat liver preparation.[2,6] Consequently BSP

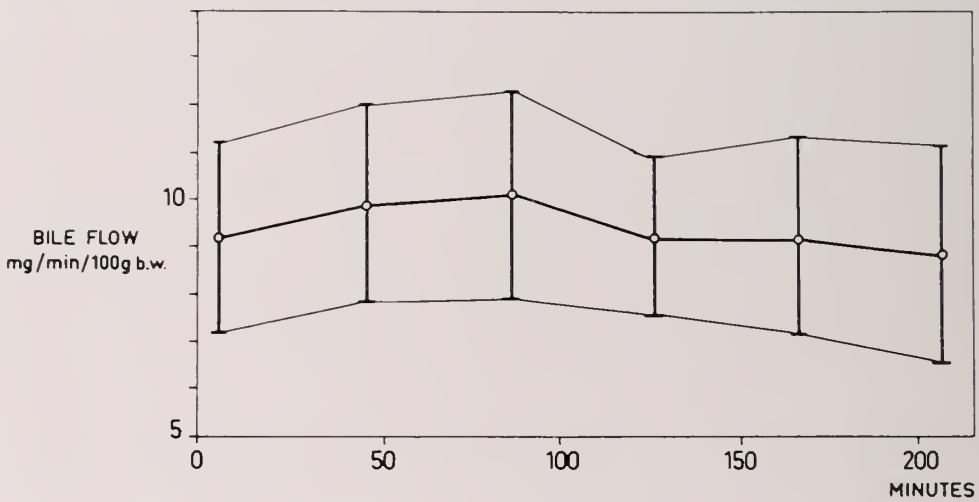


Fig. 4—Bile flow (mean ± 1 SD) during 210 minutes in eight Wistar rats receiving 0.15 M NaCl infusion (50 μl/min/rat).

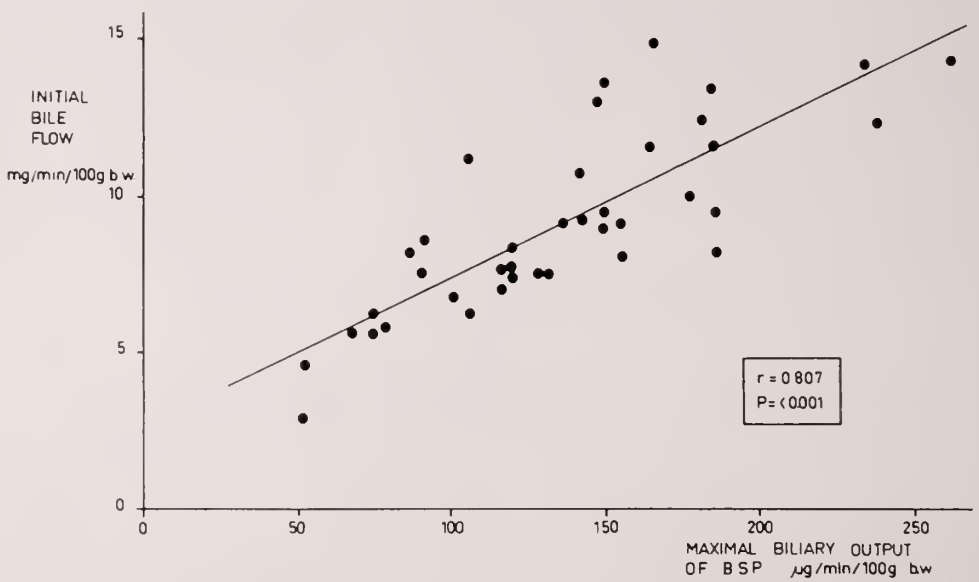


Fig. 5—Relationship between initial bile flow and maximal biliary output of BSP in Wistar rats. Bile flow shown is the mean bile flow of the initial 50- or 60-min period before the start of BSP infusion. BSP output shown was measured during the 10- to 30-min period after the start of the infusion.

Tm can be difficult to measure in the rat. The effect of BSP on bile flow is surprising if one considers that for a phthalein dye highly concentrated in bile, the expected effect would be a rise in bile flow by an osmotic mechanism;[25] such a choleretic effect can actually be observed in the dog.[18]

The effect of BSP on bile flow and Tm appears to vary not only with the different animal species, but also with the strains of rats: in Sprague-Dawley rats, infused with large doses of BSP during 90 minutes Klaassen and Plaa noted no change in bile flow.[20] Moreover, in this laboratory, differences between two strains of rats (Wistar CF and Charles River CD) could be observed; the decrease of choleresis was greater in Wistar CF rats than in Charles River CD (unpublished data).

The fall in bile flow can be partly explained by a decrease of bile salt excretion rate. Bile salt excretion rate of BSP-infused rats was significantly lower than that of control animals; this fact could be the result of a "competition" between these two organic anions simultaneously excreted into bile.[15] However, the decrease of bile salt excretion by itself does not seem sufficient to explain the large drop in bile flow. In these experiments, the fall in bile salt output was only slightly higher in BSP-infused rats than in control rats, whereas the fall in bile flow was considerably larger (Table 5). Evidence has recently been given in support of the postulate that bile in the rabbit is composed of two fractions: one would be due to the secretion of bile salts in bile; the other, quantitatively larger, would be independent of bile salt secretion.[13] The discrepancy between the large fall in bile flow and the comparatively small decrease of bile salt excretion suggests: (1) that rat bile, like rabbit bile, includes a large bile salt-independent fraction, and (2) that BSP inhibits this fraction. Moreover, inhibition of this fraction in the rabbit by rose Bengal, a structurally related compound, is consistent with this hypothesis.[10]

The indirect method proposed by Wheeler, Epstein, Robinson and Snell[27] for determining BSP Tm has been validated in the dog. However, this method has also been applied to the rat by others.[9] In this species, the effect of BSP on bile secretion could make an indirect method unreliable.

When BSP was infused, a decrease of the percentage of BSP conjugates in bile could be observed. Although there is no evidence that conjugation between BSP and glutathione is necessary for dye transfer into bile, it seems that BSP excretion may be facilitated by conjugation.[8] The decrease of conjugation could partly explain the fall in BSP excretion; however, this decrease of conjugation cannot explain the fall in bile flow. Decrease of BSP conjugates in bile is probably the result of a fall in hepatocytic conjugation; a depletion of hepatic glutathione following BSP administration was recently found in the rat.[11] However, simultaneous infusions of BSP and glutathione slightly increased the percentage of conjugation in bile, without any corresponding increase in BSP biliary excretion rate.[2]

The second criticism can be applied to rats and other animal species. It appears that maximal biliary excretion rate of BSP is not a constant parameter, but is closely dependent on variations of choleresis: (a) in several animal species, it was observed that the rise in bile flow following bile salt infusion increased BSP Tm[5,6,17,22,23]; in this work, the same effect was observed in the rat; (b) in these experiments, bile flow and BSP Tm decreased simultaneously; (c) there was a highly significant correlation between BSP Tm and initial bile flow in the rat; however, it seems that only changes in *canalicular* biliary production influence maximal excretion rate; secretin administration which in the dog produces a choleresis originating from bile ductules, or duct, has no effect on BSP Tm.[22]

There are two possible hypotheses to explain the change of BSP Tm in relation to bile flow: (a) the limiting factor in BSP transfer is not the biliary excretion rate, but the concentration of BSP in bile; BSP biliary concentration would then be constant and BSP output would be directly dependent on variations in bile flow[22]; (b) there is a maximal transport and, in addition, back diffusion from bile to hepatocyte (or plasma)[1,14,23]; the latter could be dependent on the concentration gradient between bile and hepatocyte (or plasma),[1] and an increase in water movement into the canaliculi would decrease the back diffusion of BSP.[23]

Finally, BSP Tm and bile flow varying at the same rate, BSP biliary concentration is

relatively constant; the concept of maximal concentration in bile would appear more appropriate than that of maximal transport to characterize the excretion of this phthalein dye.

The relationship between choleresis and maximal transport appears not to be valid for all organic anions excreted in bile: the Tm of rose Bengal in the rat, for example, seems independent of changes in choleresis.[4]

Summary

It is generally accepted that, as in the case of bilirubin and bile salts, the rate at which dyes are excreted by the liver into the bile has an upper limit, known as the maximal transport. The object of this paper is to present a critical study of BSP maximal transport in rats (Wistar CF). All experiments were performed at a constant BSP infusion rate, exceeding its maximal excretion rate into bile (235 to 350 μg per 100 g body weight per min). The following results were observed: (1) bile flow rate and BSP biliary excretion rate diminished progressively; after infusion for 140 minutes, bile flow had fallen by 62% and BSP excretion by 72%. The fall in bile flow was only partially attributable to reduced excretion of bile salts. (2) It became evident that the BSP excretion rate was not constant, but was directly proportional to the bile flow rate: (a) a highly significant correlation was found between the BSP "maximal" biliary excretion rate (measured at the beginning of the infusion) and the basic bile flow rate; (b) BSP excretion and bile flow diminished in parallel as the experiment proceeded; (c) as in other animal species, administration of bile salts increased choleresis and BSP "maximal" transport simultaneously. BSP concentration in bile remained practically constant during (b) and (c).

These results raise two criticisms of the concept of maximal transport of BSP in the rat. (1) The maximal transport falls progressively during infusion and is in consequence difficult to measure; however, the importance of this effect seems dependent on the strain of the rat. (2) The maximal transport depends closely on variations in choleresis and is not a constant parameter. The concept of maximal concentration in bile would appear more appropriate to the excretion of this phthalein dye than that of maximal transport.

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He has lived well and happily who has lived in the hearts of his friends.—Christopher Bannister

Current Practice of Renal Transplantation

At the University of Minnesota*

RICHARD L. SIMMONS, M.D.;† CARL M. KJELLSTRAND, M.D.;
THEODORE J. BUSELMEIER, M.D. and JOHN S. NAJARIAN, M.D.†

KIDNEY TRANSPLANTATION has become the treatment of choice for persons with terminal renal failure. Chronic hemodialysis is extremely useful but carries with it a mortality equal to, or greater than, that following renal transplantation, and is far less successful in the total rehabilitation of the patient. Chronic hemodialysis should be reserved for those patients who (a) refuse transplantation, (b) are presensitized to transplantation antigens, or (c) have rejected prior kidney transplants. Many patients in the latter group will be able to be transplanted a second time, but this procedure remains an experimental one.

Figure 1-a shows the current and past success rate at the University of Minnesota. Since 1968, transplantation from living related donors (sibling, parent, child, uncle, aunt, cousin) has resulted in renal function adequate to sustain life two years later in 90 percent of all patients. Transplant loss after two years is gradual, and it is likely that most patients who have good function for more than two years will continue to have excellent function for an indefinite period. The improvement of these statistics in the last three years has been dramatic; survival of kidneys has improved almost 40 percent when compared with the results of the 1963-1967 period.

Figure 1-b shows functional survival of kidney allografts from unrelated (cadaver) donors before and after January 1968. Whereas kidneys from living related donors have a 90 percent chance of surviving two years, only two thirds of recipients of cadaver kidneys have normal two-year function. This, however, represents a dramatic improvement from the 20 percent success rate achieved prior to 1968.

Recipient Selection

Medical and social criteria have long excluded thousands of patients from dialysis and transplantation because of fear that the psychological, surgical, and immunosuppressive stress would not be tolerated. At the University of Minnesota the only patients who are excluded are those with widespread malignancy. Since January of 1968, 107 patients have been transplanted. Mortality in the first 90 days following renal transplantation was less than 1 percent. These patients included 20 over 45 years old; 17 under 15 years old; seven with diabetic glomerulosclerosis; one with lupus nephritis; two with recent myocardial infarctions; two with overt psychosis at the time of referral; two with neurogenic bladders, and one with cystinosis. The mortality rate and functional failure rate has not differed from ideal-risk patients, age 15 to 45, with no systemic disease and normal lower urinary tracts. Eighty-five percent of all patients were working or in school three months after transplant.

Several groups of patients have become favorable candidates for transplantation despite earlier reservations.

Diabetes

Since replacement of a kidney does not correct the basic disease process, diabetics have been traditionally excluded from most transplantation programs. Of the seven patients transplanted at the University of Minnesota all but one (technical failure) are well with normal renal function. Severe peripheral neuropathy (thought to be of diabetic origin prior

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to transplantation) has almost completely disappeared in two patients. In two other patients moderate to severe retinal changes have been ameliorated. Diabetes is not a contraindication to transplantation.

Psychosis

Even experienced psychiatrists are unable to evaluate the psychosis associated with the stresses, both psychological and physical, of terminal uremia. Unless there is a long history of preexisting psychosis or severe mental deficiency, one cannot exclude a patient from a treatment as successful as renal transplantation just because of the psychological response to his disease. Two patients who had been excluded from other transplant and dialysis programs because of psychotic tendencies (one catatonic) were transplanted at the University of Minnesota Hospitals. They received some psychiatric therapy, and both are now at work, full time, without current psychiatric support.

Children

Children have been excluded from some transplantation programs because of difficulty in performing hemodialysis, fear of their psychological response, and the knowledge that immunosuppressant drugs interfere with normal growth. However, transplanted children grow at 70 percent of the normal rate and large growth spurts may occur. An 11-year-old patient with cystinosis and renal rickets grew seven inches in the first year following transplantation. Transplantation for children more than three years old should be routine.

Abnormal Lower Urinary Tracts

Patients with abnormal lower urinary tracts do as well as patients with normal lower urinary tracts, if the defects are corrected prior to transplantation. Bladder neck obstructions and refluxing ureters should be removed. Even if the bladder is nonfunctional, ileal bladders should be made. Eight patients at the University of Minnesota have received transplants to ileal bladders because of neurogenic bladder dysfunction. Six of these patients were transplanted prior to January 1968; three are alive and well with normal renal function. The other two received their transplants after 1968, and both are well.

Glomerulonephritis

Most patients who receive renal transplants have had "glomerulonephritis." It is difficult, however, even on careful histologic study, to differentiate one type end-stage kidney disease from another. Even the more well defined types of "autoimmune" glomerulonephritis respond well to transplantation. Recurrent glomerulonephritis in the transplanted kidney is inhibited by immunosuppressive drugs. Nevertheless, patients with rapidly progressive glomerulonephritis associated with antiglomerular basement antibodies (Goodpasture's syndrome) should undergo nephrectomy and be maintained by hemodialysis until the antibody titers disappear.

Malignancy

A number of patients with bilateral Wilms's tumors have received renal allografts. Hemodialysis should be continued for a year or more, to rule out metastatic disease, before transplantation.

Donor Selection

The Related Donor

The long-term results of renal transplantation dictate that, when possible, related donors should be utilized in preference to cadaver donors. The advantages of a related donor are explained to the potential recipient, who knows which member of his family he can ask and which he cannot. About two thirds of all patients will obtain volunteer related donors. The living related donor must be in perfect health and fully informed of the risks of the procedure; prospective donors rarely withdraw after volunteering. Fellner and Marshall have carefully documented the psychological rewards to the donor.[1]

Tissue Typing and the Related Donor

One must never transplant an A, B, or AB kidney into a recipient with isohemagglutinins to these antigens.

Similarly, some patients become immunized (by transfusion, pregnancy, or previous organ rejection) to tissue transplantation (histocompatibility) antigens in the prospective donor. The sera of these recipients are cytotoxic to donor lymphocytes. Cross matches should be performed at the time of the initial donor selec-

tion and should be repeated on the day before transplantation, since immunity can develop during that time. Although successful transplants have been achieved in the face of positive cross matches, these transplants are more often rapidly rejected and should not be performed.

A more delicate question is whether histocompatibility differences between related donors and recipients contraindicate transplantation. A single complex genetic locus (the HLA locus) governs the determination of the major (but not all) histocompatibility antigens in man.[2] Because of the mode of genetic inheritance, 25 percent of siblings will be identical with respect to these major histocompatibility antigens; hence transplantation between such siblings is almost uniformly successful with minimal immunosuppression. Other siblings who differ by one or more histocompatibility antigens are less successful donors but, with proper immunosuppression a high degree of success can be expected from *all* related donors (Figure 1a). Although the best potential match should be selected, it is dangerous to exclude any related volunteer in the hope that a cadaver donor of better match will appear. The statistics strongly support that *any* related donor is better than the best match cadaver.

The Cadaver Donor

When there is no related donor available, cadaver kidneys must be used. Terasaki has shown that there is no correlation between histocompatibility matching and the results of cadaver transplantation.[3] Until tissue typing is improved, one should select the best histocompatibility match between the potential donor and one's potential recipient. All available kidneys should be used since they are in short supply. It is now possible to cool and ship kidneys from hospital to hospital if no recipients are available at the site of harvest.[4]

Cadaveric organs are usually obtained from persons dying following head injury or spontaneous cerebrovascular accidents. In the past few years a definition of cerebral death based on neurological and electrophysiological parameters has been established and accepted by the medical and lay community. In most institutions a committee of physicians including neurologists and neurosurgeons, independent of the transplant team or referring physicians, act to determine cerebral death. In this way it has been possible to eliminate the ethical considerations in donor selection among cadavers.

Most states have now passed the Uniform Anatomical Gift Act which permits one to

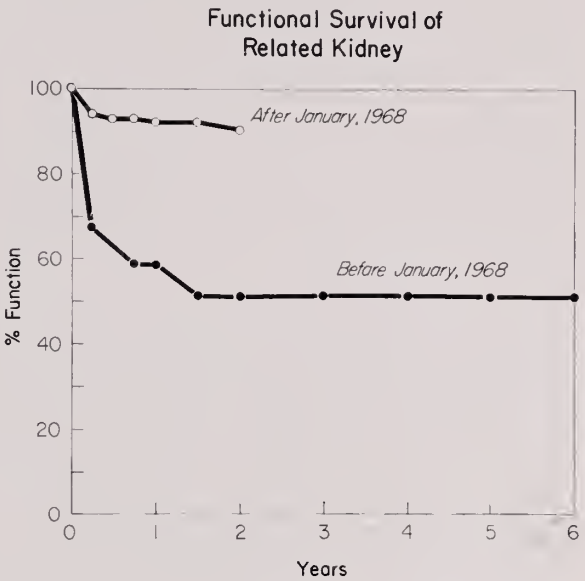


Figure 1-a—Functional survival of related kidneys receiving renal transplants before and after January 1968 at the University of Minnesota Hospitals. There has been dramatic improvement in long-term functional results. Note that the improvement in results is primarily due to the prevention of functional loss in the first three to six months following transplantation.

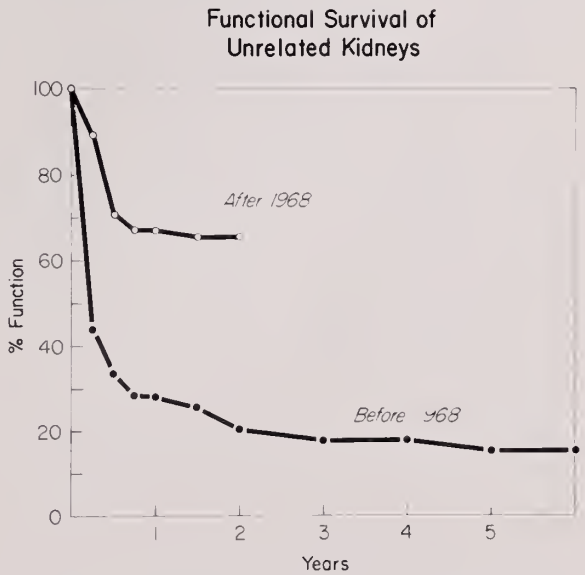


Figure 1-b—Functional survival of unrelated kidneys receiving renal transplants before and after January 1968 at the University of Minnesota Hospitals. Unrelated kidneys function less well than do related kidneys. Nevertheless, the same percent improvement is seen since 1968.

donate one's organs after death without concurrence of the next of kin, and the National Kidney Foundation is actively participating in the distribution of these organ donor cards.

Two other considerations are of importance in the selection of cadaver donors. The donor must not be able to transmit any infections or malignant disease to the recipient and he must have had adequate renal function prior to cerebral death. It is frequently possible to maintain good renal function in the prospective cadaver donors even after determination of cerebral death; in this way ischemic times can be minimized and early renal function facilitated.

Operative Technique

The donor kidney is placed in the retroperitoneal position in the iliac fossa; vascular anastomoses are performed to the host hypogastric artery and external iliac vein. The renal pelvis can be anastomosed to the recipient ureter, or the donor ureter implanted in the bladder. The latter technique is far safer.

The kidney from the living donor should be functioning until the moment of removal; the warm ischemic time of cadaver kidneys should not exceed one hour. All kidneys should be removed gently and cooled rapidly. Cold ischemic times of 12-24 hours can be tolerated, although a period of posttransplantation anuria may precede restoration of renal function.

The Prevention of Death Following Renal Transplantation

Between 1963 and 1967 there were 42 deaths in 80 patients receiving kidney transplants at the University of Minnesota, 29 of these in the first 90 days. Since January 1968, there have been only 12 deaths in 107 transplant recipients, only one of which occurred during the first 90 days. The improvement in operative mortality is a major factor in the improvement in renal function survival. Several important factors were responsible for the high mortality in the early days of transplantation. Correction of these factors has been responsible for the current low mortality despite selection of high-risk patients.[5]

Imperfect Hemodialysis in the Early Days of Renal Transplantation

The potential renal recipient is now dialyzed for several weeks prior to transplantation, so that when he is transplanted he has the best possible fluid and electrolyte balance. Interstitial pulmonary edema due to inadequate dialysis was a frequent predisposing factor for fatal postoperative pneumonia prior to 1968.

Removal of Infection Prior to Immunosuppression

All potential sources of infection must be removed prior to transplantation. In particular, dialysis-shunt infections must be avoided, and infected kidneys and ureters must be removed. The bladder can be sterilized by antibiotic irrigations after removal of refluxing ureters.

Staging the Operative Procedures

Eighty percent of the patients who died of infectious complications prior to 1968 underwent a single operation, transplantation plus bilateral nephrectomy. It is better to perform the nephrectomy several weeks before transplantation, thus minimizing operative trauma at the time of maximum immunosuppression.

Technical Factors

About 30 percent of the transplantation patients who died of sepsis prior to 1968 developed leakage from the urinary tract frequently followed by wound infection and disseminated sepsis. Since 1968 only 4 percent of the patients developed such leakage. One of these patients represents the single postoperative death in our last 107 patients. It is mandatory to avoid urinary leakage in order to prevent death.

Role of Rejection in the Prevention of Deaths

Recipients of cadaver renal transplants do less well than recipients with living related donors (Figures 1-a and 1-b), as organs from unrelated donors elicit more frequent and more vigorous rejection reactions, thereby setting up a vicious cycle in which vigorous immunologic rejection of the graft requires such a large dose of immunosuppressive drugs that the patients become susceptible even to saprophytic organisms. Donor selection from among volunteer living donors will result in a better survival rate. In addition, the use of antilymphocyte globulin for short periods of time has greatly

lowered the incidence of rejection episodes, thus reducing the incidence of opportunistic infection.

Restricting the Dose of Immunosuppressant Drugs

Since 1968, the doses of immunosuppressive drugs have been strictly limited. No patient ever receives more than 3 mg/kg of azathioprine after the first week. Azathioprine dosage is also vigorously and rapidly reduced following any deterioration of renal function. Renal functional deterioration is frequently followed by leukopenia associated with azathioprine intoxication. Prednisone is never given in a dose greater than 2 mg/kg/day, and such doses are used for less than one week. Maintenance doses of prednisone are usually less than 0.3 mg/kg. Only in this way can infectious complications associated with immunosuppression be reduced. Renal allografts which require repeated courses of steroids should be removed, rather than risk severe infections and death.

Effect of Early Renal Function

Renal failure interferes with the detoxification of azathioprine. Thus, prior to 1968, acute tubular necrosis in the posttransplant period was frequently complicated by neutropenia and infection. Acute tubular necrosis in the transplant recipient can be easily avoided by attention to the renal function of the donor during nephrectomy.[6] If temporary renal failure does occur, the azathioprine dosage must be reduced.

Prevention of Rejection

Azathioprine (a derivative of 6-mercaptopurine) and prednisone are, together, usually successful in preventing the total rejection of renal allografts from related living donors. In order to obtain good results after cadaver transplantation, antilymphocyte globulin (ALG) is probably necessary. Antilymphocyte globulin used at the University of Minnesota is prepared in horses or goats against pure cultured human lymphocytes. No anemia, thrombocytopenia, or deposition of the antilymphocyte globulin on the glomerular basement membrane of the transplanted kidney is encountered with this agent. Used by itself, it can induce two to three-fold prolongation of unrelated human skin grafts,[7] and its immunosuppressive potency is further augmented by addition of safe doses of azathioprine and prednisone. The effect of increasing doses of antilymphocyte globulin on the survival of renal allografts from unrelated cadaver donors is shown in Figure 2. Eighteen patients have now received a dose of 30 mgm/kg daily for two weeks. The only two failures in this group have been a hyperacute rejection due to preformed antibody in one patient and a technical failure in a second patient. The remaining 16 renal allograft recipients are living and well with normal renal function.

Although antilymphocyte globulin is effective in treating certain rejection episodes following transplantation, it is not as effective as prednisone. Its use as adjuvant prophylactic therapy, however, has reduced the incidence of the rejection episodes which require prednisone therapy. In this way it acts to prevent infection as well as rejection.

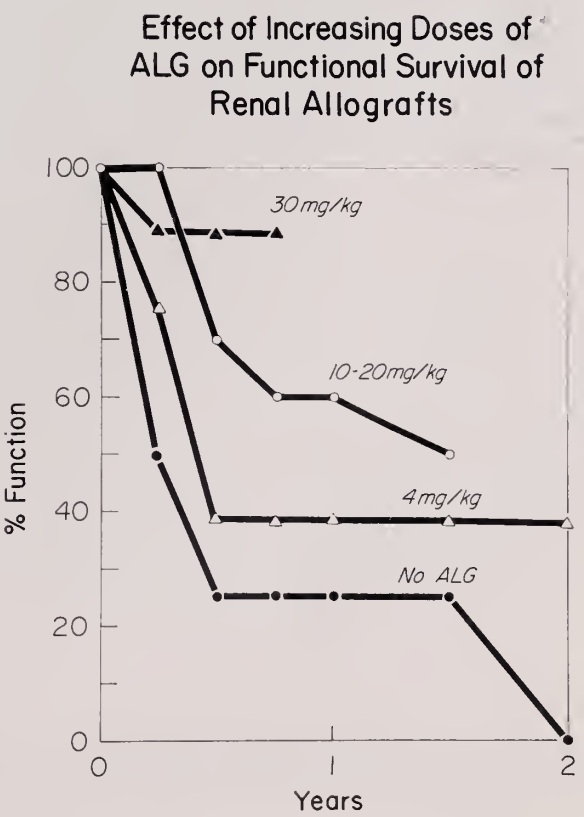


Figure 2—Effects of increasing doses of antilymphocyte globulin on the functional survival of renal allografts from cadaver donors. A two-week course of high dose antilymphocyte globulin in addition to standard doses of azathioprine and prednisone prevents total rejection of almost all cadaver kidneys.

Problems That Remain

Malignancy in Transplant Recipients

Patients on chronic immunosuppression therapy have been found to develop malignancies in far higher incidence than the remainder of the population.[8] The incidence of such malignancies may approach 5 percent. The most common malignancy found has been reticulum cell sarcoma and other lymphomas, although epithelial tumors have also been detected. The superficial epithelial tumors are amenable to standard surgical or radiological therapy, but the deeper malignancies have been refractory to such treatment. It is doubtful, however, that the incidence of malignancy will become high enough to contraindicate renal transplantation. Nevertheless, it remains a major problem requiring further work on developing methods of producing specific immunologic nonreactivity to the antigens on the kidney, without reducing the ability of the body to respond immunologically to its own mutant cells.

Second Transplants

Patients who have rejected their first transplant are frequently immunized to the antigens of the initial donor. Many of these patients who have received kidneys from related donors can receive a kidney from cadaver, or even related donors with different histocompatibility antigens. However, patients who have received kidneys from unrelated donors are frequently sensitized against a large number of persons in the general population; thus, they may not be able to tolerate a second transplant if one is necessary.[9] Such patients, however, can be frequently maintained on chronic hemodialysis, or on home hemodialysis.

Chronic Rejection

A number of patients with apparently successful renal transplants develop progressive narrowing of the renal vessels and deterioration of renal function. One cannot subject these patients to repeated courses of prednisone therapy in attempts to reverse this process, for, in so doing, one renders the patient highly susceptible to subsequent infection and death. Patients who do not respond to three successive courses should undergo transplant nephrectomy to be retransplanted or dialyzed.[10]

Cost

An average renal transplant costs $13,000. The costs of hospital care are increasing but those of transplantation are decreasing. Hospitalization time has been reduced to two weeks for most transplant recipients at the University of Minnesota. With the reduction in rejection episodes it will be possible to transplant a kidney for less than $10,000. The wide publicity given to the high costs has undoubtedly resulted in the failure to refer many patients to transplant centers. One cannot withhold such a successful treatment for economic reasons only; hence some method of payment must be devised.

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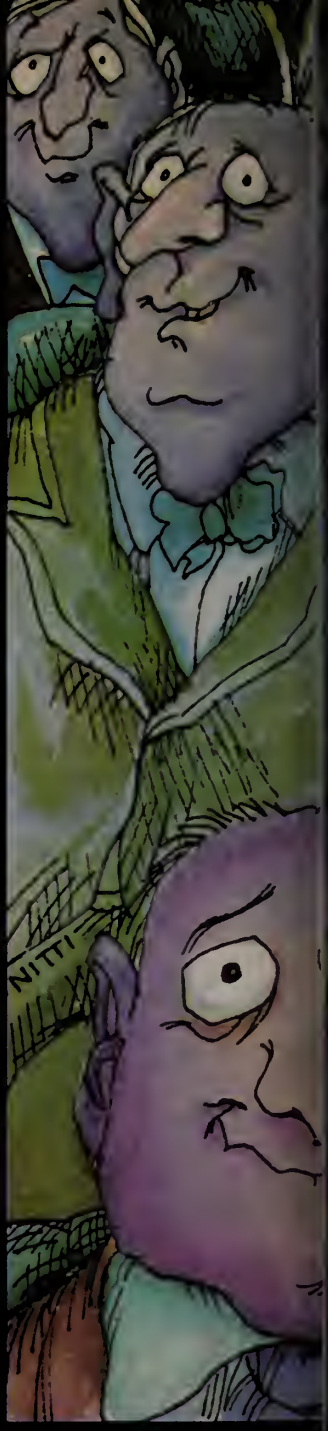
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2-5 yr. . . . . 1 tsp. t.i.d. (6 mg.)
5-8 yr. . . . . 1 tsp. q.i.d. (8 mg.)
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Editorials

A Paris Issue

When dr. rice suggested to me, at one of his delightful garden parties, that I initiate a special Paris issue of MINNESOTA MEDICINE, I was rather surprised. The idea had not occurred to me previously, but the more I thought about it, the more I had to think of several reprint requests from Clichy, France, which had aroused my curiosity. They had come from the Research Unit for Physio-Pathology of the Liver at the Hôpital Beaujon at Clichy, a northern suburb of Paris.

Previous visits to similar units in Paris proper and another one in a southern suburb had impressed me as focal points of medical progress. Reflecting further, that our knowledge of the development of French medicine had not kept up with actual events in France, I agreed to an attempt to interest the members of this research unit in a special issue of MINNESOTA MEDICINE. At the same time I was anxious to visit such an unusual unit, which also contains a special care unit for liver diseases and gastrointestinal hemorrhages.

I had never been in the suburb of Clichy before. The Metro station "Porte de Clichy" had indicated to me years ago that there was such a community in the northern "banlieue." I also remembered the "Place de Clichy" on the Montmartre and its monument to Moncey, commemorating the heroic past of that square. I found the Hôpital Beaujon to be a huge complex of an estimated 2000 to 3000 beds, and on its grounds a pleasing modern structure, the "Unité de Recherches de Physio-Pathologie Hépatique." There I had the pleasure of meeting its delightful and well known Chief, Professor Fauvert, and his enthusiastic staff. Not until several months later, when the manuscripts arrived in Minneapolis, did I realize that many of the members have an excellent command of the English language. Their manuscripts were in English and needed no revision.

The papers in this issue represent a kind of command performance on short notice and should be appreciated in this light. Special recognition is due to Dr. Christian Sicot, who acted most effectively as coordinator. All of the articles in this issue originated from the same hospital, and all but one from the "Unité de Recherches de Physio-Pathologie Hépatique." The one exception, the contribution by Professor Darnis, originated from the service of Professor H. P. Klotz.

All told, Dr. Rice's suggestion resulted in a delightful and educational experience for me, and I hope that Minnesota physicians have gained new friends. On our part, we shall be delighted to receive our new friends in Minnesota, should Professor Fauvert or any of his staff come to visit the U.S.A.

Horace H. Zinneman, M.D.
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Medical Research in France

THIS SPECIAL ISSUE of MINNESOTA MEDICINE has been dedicated to some of the work which originates from the Research Unit of Physio-Pathology of the Liver of the Hôpital Beaujon, (Paris, France). My associates and I are pleased with the reception which has been accorded us. It may be useful to introduce this unit in the frame of the organization of clinical research in France, which has undergone profound changes due to reforms which were instituted several years ago and are still in the process of completion.

The traditional organization of University—and hospital—medicine was historically divided into two parallel channels: on the one hand, the Faculty of Medicine, a university branch, which had the responsibility of theoretical teaching; on the other hand, the hospitals, which took care of the clinical teaching under a separate and autonomous administration. This separation had as many inconveniences in regard to the separate careers of hospital and teaching physicians as it had for the teaching itself.

A reform which had been worked out under the leadership of Professor Debré in 1958 succeeded with a fusion of the two types of instruction by means of the creation of hospital and university centers, which were charged with the teaching of medicine as well as with the care of the sick and with medical research.

As far as Paris is concerned, the university, which had reached gigantic proportions, had more recently been divided into 11 autonomous universities, where the various Parisian creations of hospital and university centers were integrated.

An important factor of this reorganization is the *Institut National de la Recherche Médicale* which is the French counterpart of the American *National Institute of Health.*

The Institut National de la Recherche Médicale has established research units in the various hospital and university centers, built the research buildings, financed equipment, maintenance, and also technicians of various grades, and taken charge of the career investigators, who were not integrated into the creation of hospital and university centers.

Thus, our unit, which pursues clinical research in hepatology, owns a building of 2,250 square meters, equipment, technicians and a working budget, all of which are furnished by *Institut National de la Recherche Médicale.* In addition, the administration of the Paris hospitals (assistance publique) created an agency for the development of clinical research (Association Claude Bernard). It supplies us also with positions for investigators and technicians. The *Commission de Pathologie Expérimentale du Centre National de la Recherche Scientifique* also furnishes means for equipment as well as for personnel. Finally, a private association, *La Foundation Nationale pour la Recherche Médicale,* contributes additional funds for those functions which are not covered by official sources.

The uniqueness of the Research Unit is its close association with a medical subspecialty service of liver diseases which includes a special care unit for severe hepatitis. The buildings are adjacent, and all of the investigators of the research unit take part in clinical and research pursuits. The subjects of research are mostly mixed, covering clinical developments as well as experimental work. The research unit contains several sections: hepatoportal hemodynamics (with close surgical cooperation), enzymology, studies of biliary secretion, pathology and electronmicroscopy, electronics and radioisotopes and finally biochemistry.

The personnel consists of 15 investigators, among them several foreign assistants with appointments for one or two years, and 15 technicians of various grades.

As you may see, the goals and the problems of medical research are similar in France and the U.S.A., in spite of different organizational structures. One of the most gratifying results is the friendly and close relationships which we entertain with the research groups of our specialty in the U.S.A., and in particular in New York, Boston, and Los Angeles, as well as personal acquaintances, made possible by our participation in meetings which were organized by the *American Association for the Study of Liver Diseases.*

Professor R. E. Fauvert
Paris, France

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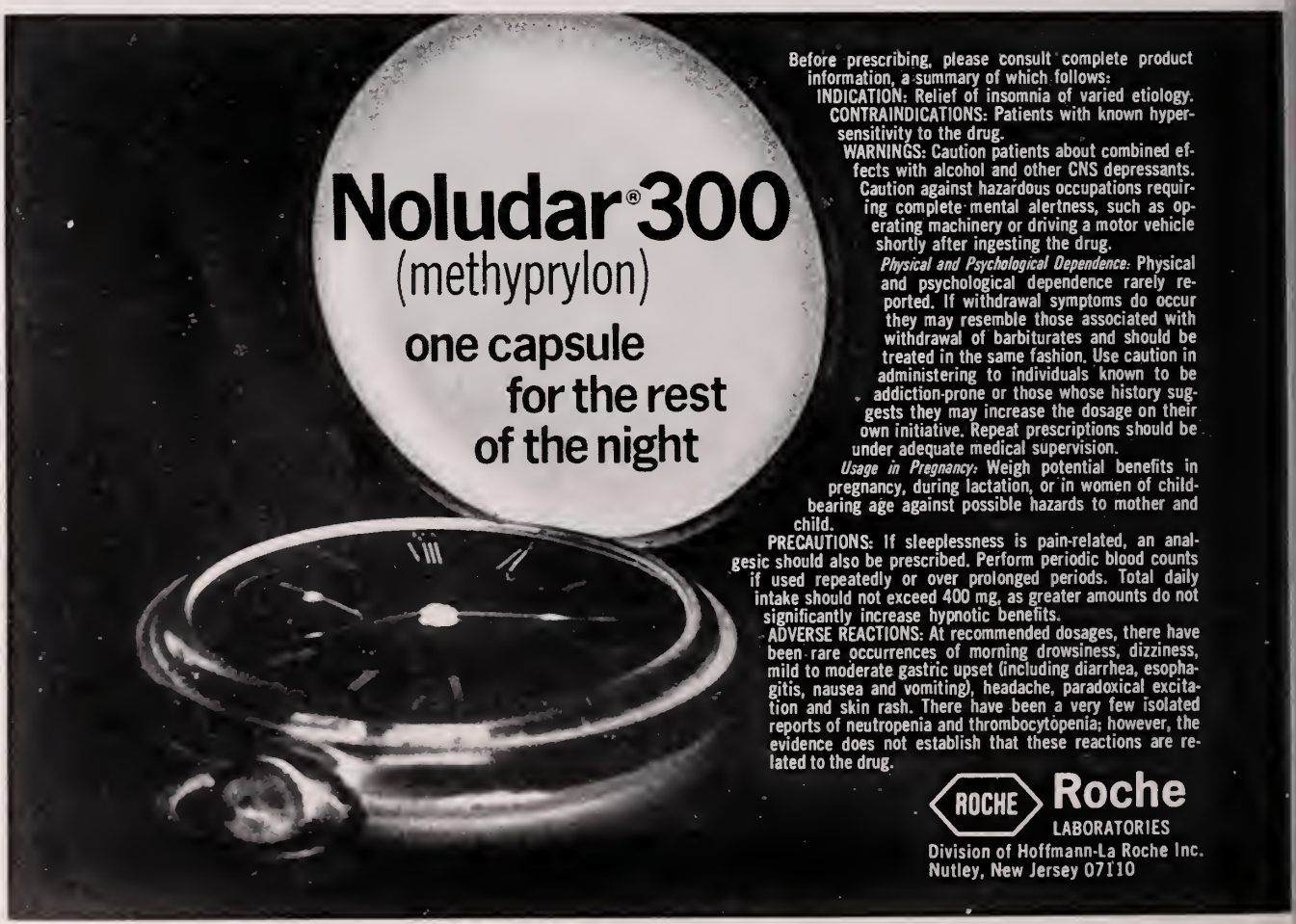
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Portal Hypertension in the Absence of Cirrhosis or Extrahepatic Portal Vein Occlusion

The article, "Portal Vein Thrombosis in Intrahepatic Block" by Sicot, Sakellaridis, Rueff, Maillard, and Benhamou,[1]* emphasizes the difficulties in diagnosis and treatment of this combination of conditions. The complication of portal thrombosis in cirrhosis of the liver with or without hepatoma is well recognized, but its occurrence in congenital hepatic fibrosis and in hepatoportal sclerosis is more unusual. In congenital hepatic fibrosis, it is generally held that the intrahepatic block is presinusoidal and is the result of either hypoplasia of the portal vessels or their compression by the periportal fibrous tissue.[2] In the rare condition, "hepatoportal sclerosis" with a patent portal vein, the intrahepatic block also appears to be presinusoidal but the histologic alterations are more subtle and the liver biopsy may be reported as normal.

In a large series of cases reported by Mikkelsen et al.,[3] in which the histopathologic alterations were carefully studied, the initial liver biopsies revealed a derangement of the hepatic lobule characterized by the presence of several dilated central veins, some of which were close to the portal regions. Two or three portal triads were close together in one area, yet in another they were widely spaced. Scattered portal areas were greatly enlarged by the perivascular and periductal deposition of collagen. The limiting plate was usually intact except in smaller portal tracts where it was partially disrupted. Dilated vascular spaces and, frequently, more than one arterial branch usually occupied the abnormal portal triads Frequently the portal vein radicles were significantly thickened or sclerotic and occasionally they could be differentiated from arterial branches only with difficulty.

Similar changes were observed in cases with total or partial occlusion of the portal vein. In the few patients who died in hepatic failure two or more years after initial presentation, at autopsy there was a striking change in hepatic architecture. The liver appeared shrunken, firm, and somewhat irregular but not nodular. Its weight varied from 700 to 1,000 gm. Histologically, the limiting plates of the portal areas were disrupted by an arachnoid pattern of fibrosis which had the appearance of sweeping through the hepatic parenchyma and entrapping segments or clumps of liver cells. The dilated and proliferated vascular spaces seen originally had disappeared. Regenerative nodules were still not apparent.

The authors[3] interpreted these histologic alterations as phlebosclerosis of the intrahepatic portal veins and coined the now accepted term "hepatoportal sclerosis" to designate the condition. It is noteworthy that the condition appears to be more common than previously noted, and large numbers of cases have been reported from both Japan[4] and India.[5] In the latter country the condition has been considered to be of such importance that the Indian Council of Medical Research[6] conducted a workshop on noncirrhotic portal fibrosis with the collaboration of five medical centers of that country. At that meeting, the hepatic lesion was characterized by varying degrees of portal scarring, sclerosis of the small intrahepatic radicles of the portal vein, atherosclerosis of the larger radicles with or without thrombosis, mild to moderate cellular infiltration, and absence of pseudolobular formation diffusely affecting the liver. It was emphasized that some of the features can be appreciated only in a deep-wedge biopsy or autopsy material and that percutaneous needle biopsy may be inadequate. Although these workers preferred the term "noncirrhotic portal fibrosis" for the lesion described, there seems to be considerable similarity to the histologic appearance delineated by Mikkelsen et al.[3] for their autopsied cases.

Although it is apparent that progress is being made on clarifying the hepatic lesion, we still do not know for certain whether the vascular lesion is the cause or the result of the portal hypertension in these cases.

Archie H. Baggenstoss, M.D.†
Rochester, Minnesota

*See page 87.
†Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
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Editor's Soliloquy

Boundaries of Medicine?

It has been stated that "the progress of mankind depends on the success with which the laws of phenomena are investigated and on the extent to which a knowledge of these laws is diffused."* Care of the sick knows no national boundaries, for human ills are fundamentally the same the world over, except, of course, for regional endemics of disease attributable to indigenous environmental and ecological factors.

To familiarize oneself with all, even with the most common human maladies would require the indefatigability and perseverance that are the hallmarks of genius. In our profession there have always been a few such dauntless seekers for whom boundaries have never become barriers. These medical Galahads are the professional colleagues we most admire and desire to emulate, for they constitute an advancing front on a voyage of medical discovery that is dimensionless. And it is from their bold thrust, adroitly and firmly directed at eventual and inevitable success, that our great-healer image is derived and universally disseminated.

In this issue—as in several past and future issues—MINNESOTA MEDICINE humbly recognizes these eminent contributors from across the seas. We are indeed proud to have our journal act as liaison between their community and ours, fostering thereby a viable spirit of international seminarship.

Wide diffusion of medical knowledge is not new; it is traditional. Galen, the eclectic, in his quest for new medical theories and therapies, traveled extensively before he finally settled down permanently to practice in Rome. His far-flung frontiers included Greece, Sicily, Phoenicia, Palestine, Crete, Cyprus, and Alexandria.

It is vital to the progress of medicine that each one of us rigorously maintain his intellectual and moral independence, free as Galen to exchange new ideas and fresh knowledge, internationally and interracially, in order to preclude any danger of a future medical recession into a Dark Age of emasculating and stultifying bureaucracy.

Rather than expending our funds and efforts in provincial machinations, calculated to erect political and legal obstacles and barriers within and between our respective communities and countries, we should continue to direct the major portion of our extracurricular activities to the educational and exchange fields of medicine, uncorrupted by and impervious to the inefficiencies and extravagances inherent in the designation of *commissionaire* with all its arbitrary and doctrinaire connotations.

The free national and international exchanges which MINNESOTA MEDICINE has initiated have made eager readers almost unanimous in their desire and determination to visit our newly-acquired friends for the rare pleasure and privilege of indulging in their favorite shoptalk eyeball to eyeball with their worthy inimitable confreres.

Carl O. Rice, M.D.

*Edward B. Vedder, A.M., M.D., D.Sc., F.A.C.S.: Medicine, Its Contribution to Civilization, 1929. Also see page 100.

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(Continued to Page 139)

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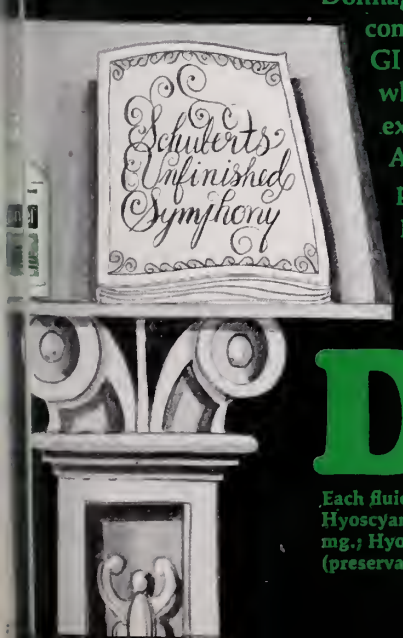
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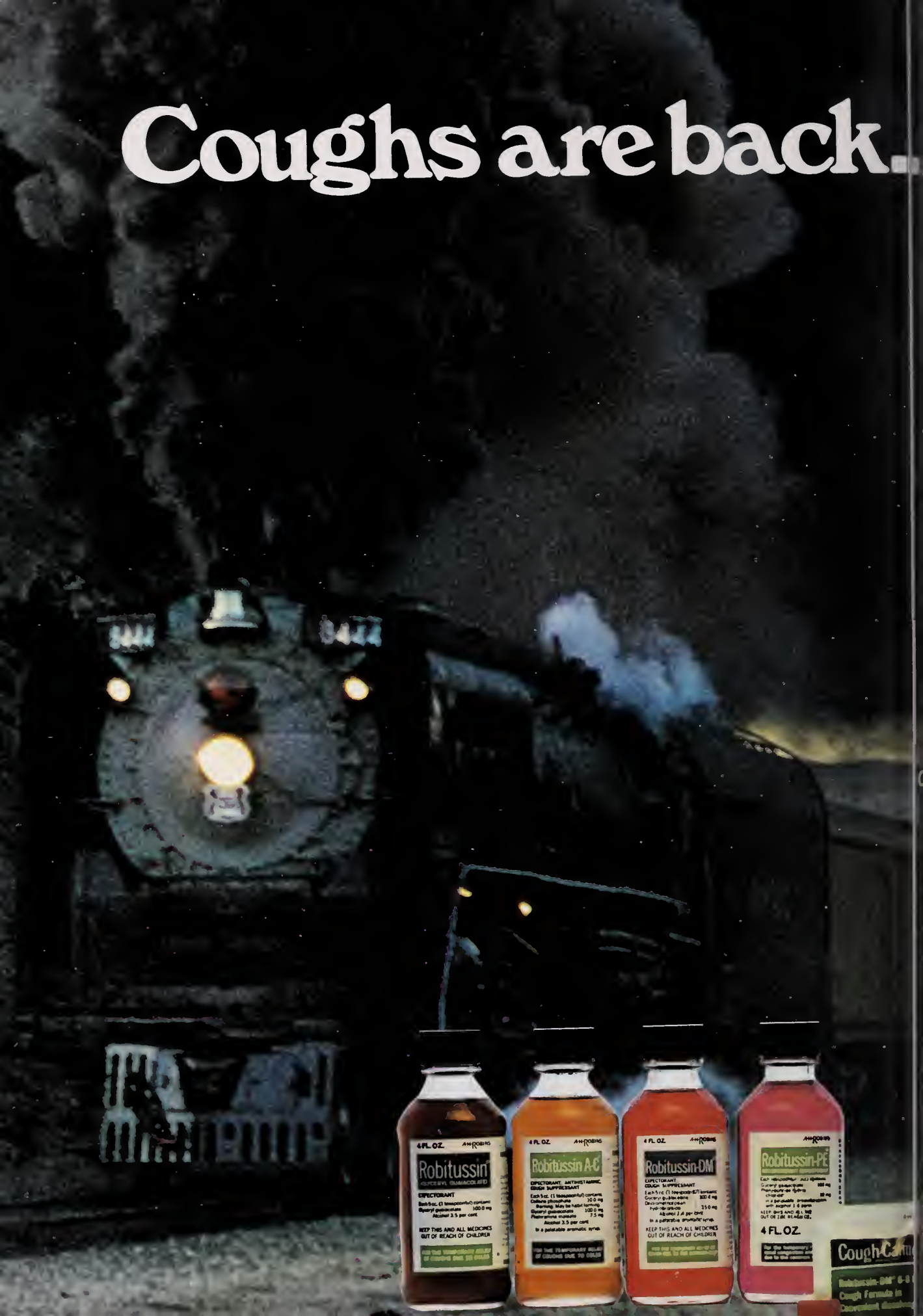
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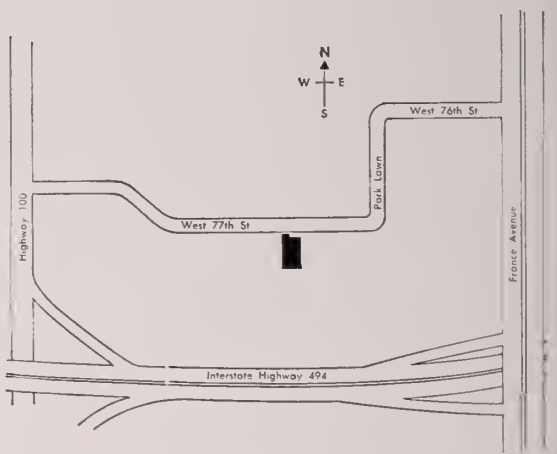
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(Continued from Page 132)

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II. PARENTERAL: Intravenous administration may be continuous or intermittent (6 to 8 hour intervals); 1 to 4 Gm. daily in adults; 15 to 25 mg./lb./day in children, depending upon severity of infection. Recommended I.M. dose is 100 mg. (2 ml.) for adults, 50 mg. (1 ml.) for children 30 lbs. or more and 1.4 to 1.8 mg./lb. in smaller children. Injections are usually given at 6 to 8 hour intervals; may be given at 4 to 6 hour intervals for severe infections.

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Review

Cirrhosis Edema-Ascites Syndrome

The Role of Hormonal Abnormalities in the Pathogenesis

F. DARNIS, M.D.*

WATER AND SALT RETENTION is one of the fundamental sequences of liver cirrhosis. During the past few decades its study has given rise to a great number of investigations, since its physiopathology represents the indispensable basis for a rational therapy.

Certain pathogenic factors have been singled out, the importance of which is controversial. These factors do lead to salt and water retention. Today we know that the excessive renal reabsorption of water and sodium is largely the result of hormonal abnormalities, in which an excess of aldosterone is predominant; but the pituitary antidiuretic hormone also plays a role. Let us see how one acquired this information by examining the facts and their interpretations.

Abnormalities in Cirrhosis with Water Retention

Extracellular Compartment Volume and Composition

The predominating phenomenon is the general extracellular hypervolemia which manifests itself most strikingly as the edema-ascites syndrome. It is important to know whether this hypervolemia involves the plasma and interstitial compartment alike, or one of the two preferentially.

One does not find as might be expected, a decrease of plasma proteins and osmotic pressure with a decrease of plasma volume and a volume increase of interstitial fluid resulting in edema and ascites, but there is an *increase in plasma volume,* even preceding the advent of edema.[7]

This augmented plasma volume, however, undergoes a reduction as the cirrhosis becomes decompensated, particularly in the terminal period of functional renal insufficiency; but even in the terminal period the plasma volume remains normal or only minimally decreased.

The *hyponatremia,* which roughly parallels the extent of water retention,[8,9] is generally known, and it should not be interpreted as iatrogenic sodium loss, (diuretics, paracentheses, low salt diet); it appears also in cirrhotics who have never been treated. This "hyponatremia" is contradictory to the increase of the total exchangeable sodium, which parallels the extracellular fluid volume. Serum *potassium is generally normal* or slightly decreased, except in the terminal phase of renal insufficiency, where it becomes frankly elevated. The *osmotic pressure* of the extracellular fluids and particularly of plasma varies with its sodium concentration and is usually decreased in these patients. There is generally a *hypoalbuminemia* in the plasma compartment. One might expect that the interstitial compartment experiences an inverse development, but this is not always true. Particularly in the ascitic fluid one can observe the widest fluctuations of protein concentration. The use of radioisotope techniques has shown that one can divide the ascitic cirrhoses into two groups: those in which the capillary permeability is little increased and the ascites contains little protein, mostly albumin, and others which, on the contrary, show a severe capillary hyperpermeability (increased by existing portal hypertension) and high protein concentration, which on electrophoresis resembles the pattern of the plasma. In these latter cases the ascites may contain as much as one third of the total exchangeable albumin.[38] Forty to 80 percent of ascitic fluid is exchanged hourly with the plasma, so that the ascites constitutes by no means an isolated sector.

The coexistence of hyponatremia, osmotic hypotony and hypervolemia should normally initiate a corrective renal elimination of water and sodium.

*Professor the College of Medicine—Physician of the Hospitals of Paris, Department of Endocrinology and Nutrition, Faculty Beaujon (Director, Prof. H. P. Klotz) 92-Clichy.

Intracellular Compartment Volume and Composition

The intracellular fluid volume of the hydropic cirrhosis has received little study. If one applies the law of osmotic equilibrium, one can expect a transfer of extracellular water into the cells, leading to an intracellular overhydration as an element of general overhydration. This is exactly what certain recent studies have found, thus confirming that an increase of total intracellular water is present in these patients.

The cellular electrolyte composition is still not well known. The potassium concentration can be estimated with radioactive potassium by determination of the amount of "exchangeable" potassium. It appears that the overall amount of *potassium is always decreased* in cirrhosis with ascites, and that this depletion reaches magnitudes of 20-30 percent of normal values.[39]

As far as the intracellular sodium is concerned, we are still dealing with hypotheses. One of these hypotheses suggests the possibility of an abnormal transfer of sodium into the cells, a hyperpermeability of cell membranes to sodium, or a malfunction of the "sodium pump." If this hypothesis is confirmed, it would explain *the paradox of hyponatremia* in patients who retain practically all the sodium they ingest.

Circulatory Abnormalities

In the course of the majority of the hydropic cirrhosis we encounter *arterial hypotension*. Frequently one can notice a remission of arterial hypertension at the time of the development of hepatic cirrhosis. This hypotension tends to be accentuated when the cirrhosis becomes severe, and particularly so in the phase of terminal renal insufficiency.

Another idea concerns the *importance of vascular shunts* in the course of hydropic cirrhosis. The best known ones are the superficial and deep portacaval and porta-pulmonary shunts.[37] Arteriovenous shunts were not recognized until recently, but they unquestionably do exist in these patients; arteriovenous pulmonary shunts,[3] systemic A-V shunts in the upper extremities, for instance, explain the high pO_2 of venous blood in the forearms. Some of these, particularly the porta-pulmonary and arteriovenous pulmonary shunts, contribute to a deficit of arterial oxygen saturation. They also tend to create an increase of the vascular bed and thus might explain part of the hypervolemia.[27]

As the cirrhosis becomes more severe, one may notice abnormal vasodilation, resulting in spider naevi, ruddy cheeks and even vasodilation of the abdominal skin.

A third concept, not shared by everyone,[39] is that of an increased cardiac output in hydropic cirrhosis.[21,22] At the stage of renal insufficiency the cardiac output decreases as a rule, but even then it often exceeds the normal range. This entire group of abnormalities (elevated cardiac output, circulatory hyperkinesia, diminution of total peripheral resistance and preferential perfusion of certain regions) should be kept in mind.

Abnormalities of Renal Function

Modified Urinary Excretion

The *reduced excretion of NaCl* is the most important urinary symptom, more so than the oliguria. At a time when ascites and edema are rapidly formed, the daily excretion of sodium is below 10 mEq; not uncommonly it drops near zero, about 1-2 mEq per 24 hours.[8]

This practically complete *retention of sodium* is generally associated with a severe oliguria with an inversion of the diurnal rhythm of elimination and resulting in nocturia. This oliguria is by no means constantly present. One may observe normal daily volumes or even polyuria in these patients. In these cases minimal excretion of NaCl is the only reminder of a hydropic syndrome. This unusual dissociation of diuresis and sodium excretion must be kept in mind. For the time being let us emphasize that a normal urinary fluid excretion does not change the basic hyponatremia in any way.[17]

In contrast with the sodium retention, the *high urinary concentrations of potassium and urea* are impressive,[9] which also explains a moderate hypomolality of the urine; and only in the phase of terminal renal insufficiency can one observe a return of renal concentration power.[87]

One should add that the described urinary abnormalities are by no means an isolated trou-

blespot; identical changes, particularly those concerning the diminished excretion of sodium, have also been found in the sweat and saliva. Thus the abnormality of sodium excretion is not just a renal problem, but it suggests a more general effect and renders the hypothesis of a hormonal mechanism more plausible. This will be discussed later on.

Osmotic Diuresis

The urinary abnormalities of hydropic cirrhosis are magnified by the administration of electrolytes and water.[17] Oliguria cannot be influenced by the administration of water either orally or intravenously. The only manner in which one can induce an increased urine excretion, is by establishment of an osmotic diuresis, for example, by hypertonic sugar solutions.[8]

Functional Disturbances of the Kidneys

The poor urinary elimination of water and sodium in hydropic cirrhosis is essentially caused by two factors: decrease of glomerular filtration and increase of tubular reabsorption. Also a third factor, the renal blood flow, should not be underestimated.

Decreased Glomerular Filtrate

The decrease of the glomerular filtration rate can be as much as 60% compared to normal subjects according to our measurements of glomerular clearance by the endogenous creatinine method.[9] A decrease of filtered water means a lesser amount of filtered sodium, and this is emphasized by the basic hyponatremia of these patients. Let us remember that the graver the hydropic cirrhosis, the greater the fall of glomerular filtration until, at the time of development of terminal renal insufficiency, the glomerular filtration amounts to no more than 20-25 ml. per minute.[41]

Hyper-absorption of Water and Sodium

In the normal person the amount of reabsorbed water is about 99% of the amount which has been filtered through the glomeruli. In the cirrhotic the percentage is still increased, by our measurements,[9] to 99.5% for water and even more so for sodium; at a time when ascites develops rapidly, the reabsorption approaches 100%. The interpretation of these results is a different matter. Is it simply the effect of diminished glomerular filtration rate, or is there an increased reabsorption which is independent of glomerular filtration? By means of administration of fluids and electrolytes[17] we believe we have demonstrated the independence of tubular reabsorption from glomerular filtration, at least for a long period of the development of the disease, and that the water and salt retention is really the effect of tubular overabsorption. At the terminal period, however, the failure of glomerular filtration is sufficient to explain the nearly total proximal reabsorption of salt and water.[32,33]

Reduced Renal Blood Flow

A reduction of renal blood flow has been emphasized more recently.[27,39] This is not a late or terminal event, but a relatively early one since certain authors reported a 14% reduction of renal blood flow even in the preascitic phase. However, beginning with the ascitic phase of ascites the renal blood flow is markedly reduced (about 50%), as is the renal fraction of the cardiac output, whereas the cardiac output itself is increased. Be that as it may, in the majority of the cases we have a decrease of renal blood flow, which directly influences the glomerular filtration rate as well as the tubular reabsorption.

Terminal Renal Insufficiency in Cirrhosis

A goodly number of hydropic cirrhoses, be they treated or not, end up in a functional renal failure, which in fact heralds the terminal period of the disease.

It is characterized by the association of progressive azotemia (often sudden and almost always irreversible), hyperkalemia, hyponatremia and severe oliguria. This syndrome often arises after an intestinal hemorrhage or after removal of a significant amount of ascitic fluid by paracentesis. This azotemic period is often accompanied by arterial hypotension. In this stage the plasma volume and cardiac output deviate from the values which were mentioned previously, but often there are normal or greater than normal values.[25,26] At this stage the vasodilation and preferential arterial supply of skeletal muscles and skin are quite obvious,[27] even though the renal blood flow has collapsed and the renal vascular resistance has

increased.

Pathologic Anatomy of the Kidney in Cirrhosis

Certain authors observed histologic changes in the kidneys of deceased cirrhotics and have tried to correlate these abnormalities with the ante-mortem clinical and laboratory data.[27] They noted, according to statistics, in variable numbers of incidence, an intercapillary glomerulonephritis. The glomerular lesions consisted of hyalinization of capillary walls and connective tissue with changes of the basement membrane. In the majority of the statistics the incidence of these lesions was hardly greater than in subjects who had died from other causes. Above all, where these abnormalities existed they were without correlation with either the hydropic syndrome or a terminal episode of renal insufficiency. Moreover, the majority of authors who have recently studied the kidneys of deceased cirrhotics, have attested to the pathologic-anatomical normalcy of these kidneys.[19a] One exception, however, concerns the rather frequent observation of a hyperplasia of the juxtaglomerular apparatus wherever there was a hydropic cirrhosis. Since this apparatus is the source of the renin-angiotensin system, we must particularly emphasize this lesion.[24]

Factors Responsible for the Electrolyte Imbalance

Since multiple factors contribute to the edema-ascitic syndrome, it will be necessary, even at the risk of being dogmatic, to separate them into three distinct categories, corresponding to the three groups discussed above. At the capillary level we have three factors: portal hypertension, hypoproteinemia and increased capillary permeability.

Portal Hypertension

Portal hypertension can theoretically lead to ascites by means of a double mechanism; venous hypertension causes a differential pressure at the level of the arteriolar-capillary junction and results in a change of Starling's isosphygmic point and an abnormal transudation. This is enhanced by the reduced osmotic pressure of the hypoproteinemic plasma.

Another mechanism is based on porta-renal anastomosis in the cirrhotic where the portal hypertension is transmitted to the renal veins. This in turn causes an increase of tubular absorption of water and sodium and an expansion of the extracellular compartment.

These arguments attributing an important role to portal hypertension should not let us forget that portal hypertension by itself is incapable of creating ascites in men or experimental animals. It is known, for instance, that simple portal vein ligation in the dog is ineffective in this respect, and if one wishes to create ascites one has to add two additional procedures: ligation of the inferior vena cava in the abdomen and plasmapheresis. It is very easy to precipitate ascites in the dog by ligation of the thoracic inferior vena cava above the junction of the hepatic veins: in other words, by creating hepatic congestion. Likewise extrahepatic portal obstruction in man, or even pre-sinusoidal intrahepatic blocks, as found in schistosomiasis, never result in ascites. If ascites does occur under these circumstances, it is always after a massive intestinal hemorrhage, which constitutes an equivalent to plasmapheresis—the sudden development of hypoproteinemia.

In man only those types of portal hypertension which also encompass blockage or hypertension of the hepatic veins (Budd-Chiari) or intrahepatic post-sinusoidal blocks (ordinary cirrhosis) or congestive failure, are strongly ascitogenic. In other words, portal hypertension has to involve the whole liver before it can cause ascites.[17]

Hypoproteinemia

The almost ever-present hypoalbuminemia in hydropic cirrhosis with a more or less reduction of the osmotic pressure of the plasma is an important factor.[7] Direct measurements of osmotic pressure of plasma could even establish an ascitogenic pressure zone. However, as one examines individual cases, contradictions begin to appear: ascites may recede spontaneously despite low plasma albumin.[7]

These contradictions, where the hydropic syndrome and protein changes evolve together, may parallel each other by pure coincidence, since they do not depend on each other. In such contradictions one could wonder whether to consider the amount of total circulating proteins, rather than the protein concentration.

One must conclude that hypoalbuminemia represents at most one factor in the hydropic syndrome. The simple diminution of albumin, as important as it may be to oncotic pressure, was never able to create ascites in the absence of hepatic disease. Moreover, intravenous administration of salt-poor albumin to cirrhotics with ascites does not necessarily lead to diminution of edema or ascites. It is true that in many of the cases much of the injected albumin ends up in the ascitic fluid, while only 25% of the injected amount is retained in the plasma. This is important and should direct our attention to another factor: the changed capillary permeability.

Capillary Permeability

Increase of capillary permeability in the course of hydropic cirrhosis has long been suspected, but the various tests proposed for the study of this phenomenon were doubtful and did not permit valid conclusions. As we have shown with R. Cachera,[6,16] only an evaluation of hyperpermeability of colloids could be meaningful in the matter. We have known for a long time, and experiments with tagged proteins have confirmed it, that under normal conditions the capillary walls permit the filtration of only a small fraction of proteins. An effective qualitative change of the capillary walls does unequivocally exist in hydropic cirrhosis. We have studied the problem of capillary permeability in hepatogenic pathology by applying Landis' test to the capillary protein loss. The results were significant, and we shall refer to them only by the statement that we observed perfect parallelism between capillary protein loss and the degree of expansion of extracellular fluids.[16]

One error has been committed too frequently in the study of hydropic cirrhosis: the introduction of a sort of competition between the three great pathogenic factors. The worst approach is the tendency to explain the syndrome with one single mechanism, whichever it may be. These physiologic abnormalities do not only coexist, but they enhance one another. Animal experimentation and human therapy show that each factor, taken alone, is really accessory in nature and by itself, unable to explain the formation of ascites. On the other hand, their simultaneous action is synergistic. Atkinson and Losowsky have also demonstrated that one can easily predict formation or resorption of ascites, if one knows the serum concentration of albumin and the portal vein pressure.

Factors Which Are Responsible for Associated Circulatory Abnormalities

The best known factor is portal vein hypertension (intrahepatic-postsinusoidal), which is directly responsible for the generalized distention of all portacaval anastomoses, for portapulmonary shunts, and probably also for generalized arterial hypotension.

But how does one explain the multiple arteriovenous shunts of the pulmonary as well as of the general circulation? As far as the general clinical aspects of these shunts (ruddy complexion, spider angiomata, etc.) are concerned, the role of estrogen excess was invoked as a consequence of diminished conjugation by the liver or hypergammaglobulinemia. As yet we have no explanation for the increase of cardiac output and circulatory hyperkinesia in the face of decreased peripheral circulatory resistance. Perhaps we are dealing here with an as yet undiscovered circulating vasodilator, which has been named VDM (vasodilating material).[29]

Factors Responsible for Abnormal Renal Function

The immediate mechanisms, but not necessarily the primary cause (we shall refer to this again) for the excessive tubular reabsorption of water and sodium, are doubtlessly hormonal. Two hormones should be kept in mind: aldosterone, which plays a fundamental and indisputable role, and the pituitary antidiuretic hormone (ADH), which is perhaps of secondary importance.

Aldosterone

Hyperaldosteronism in hydropic cirrhosis is a well established entity and confirmed by all concerned authors.[41] Aldosterone effect on renal tubules is *increased excretion of potassium and retention of sodium.* It thus favors water retention and expansion of the extracellular fluid compartment. Secretion of aldosterone is stimulated by salt-free diet, potassium excess, and decreased intravascular volume.

Regarding this last factor, one can undoubtedly object by pointing out that in the majority of all cirrhoses there is an increase of plasma volume, which would make a poor stimulus for aldosterone secretion; but this seeming contradiction is resolved when one considers a truly fundamental aspect, that of the effective circulating volume.

Numerous studies have shown that the homeostatic mechanism of aldosterone secretion depends, in the last analysis, neither on the total amount of extracellular fluid nor on the total intravascular fluid, but only on the efficient part of the latter, essentially represented by the arterial blood. Under the effect of an arteriovenous fistula, for instance, whatever its localization may be, the veins are distended and the blood volume is increased; but in spite of increased cardiac output the arterial filling remains mediocre and we find aldosteronism and sodium retention. When the A-V fistula has been closed, the cardiac output and the blood volume decrease and diuresis and natruresis follow, because the arterial blood flow, namely, the effective circulating blood volume, increases and thus no longer stimulates aldosterone secretion. Applied to hydropic cirrhosis we have a similar situation: increased plasma volume, increased cardiac output, but a significant portion of the blood mass (up to 3 liters) trapped in the vast network of splanchnic veins, resulting in poor arterial filling and aldosterone stimulation. Radioisotope techniques have shown that the hyperaldosteronism in cirrhosis is due to hypersecretion by the adrenal cortex rather than to diminished inactivation of aldosterone by the injured liver, which plays but a secondary role.

Coppage and Call[15] measured adrenal aldosterone secretion by means of tritiated aldosterone and found that in cirrhotics with ascites the daily secretion rose from 421 to 2080 μg with a corresponding urine secretion from 75 to 272 μg (in the form of the 3-oxo-conjugate). Normal controls, by comparison, who were subjected to an equivalent sodium intake, varied from 95 to 249 μg with a urinary secretion from 5 to 26 μg.

It has also been proven that there is a perfect correlation between the rate of ascites formation and aldosterone secretion. Moreover, the compounds which act either by inhibition of aldosterone production (metapirone) or by blocking its action (spironolactone) are very successful diuretics in these patients. Besides, adrenalectomy with subsequent administration of glucocorticoids is an effective treatment of ascites in cirrhotics. Let us add that volume-sensitive receptors are located also in the vena cava but mostly in the carotid arteries.

Antidiuretic Hormone

Physiology teaches us that the pituitary antidiuretic hormone is secreted by the supraoptic and paraventricular nuclei of the hypothalamus, stored in the posterior pituitary gland, secreted from there into the circulation and controlled by the osmoreceptors in the internal carotids. Thus any increase of extracellular osmotic pressure triggers hormonal secretion which, in turn, stimulates reabsorption of water in the distal renal tubules. The hyponatremia and diminished osmotic pressure of these cirrhotics should theoretically block the secretion of antidiuretic hormone. But numerous authors have observed marked increase of antidiuretic hormone in the urine, the extravascular fluids, and the serum of hydropic cirrhotics.[13] It appears then, that under these conditions the activity of antidiuretic hormones can be independent of total osmolarity; but we must remember that these physiologists also recognize that antidiuretic hormone production is likewise controlled by the volume receptors and the diminished effective (arterial) blood volume.

There is no general agreement on the importance of antidiuretic hormone in the hydropic syndrome of cirrhosis. At present there is a tendency to consider it an accessory factor, which can explain the difficulty of the cirrhotic in excreting free water at the level of the distal tubules and consequent overhydration and hyponatremia. In a recent study on the syndrome of inappropriate secretion of antidiuretic hormone, Bartter and Schwartz[2] present hydropic cirrhosis and congestive heart failure as two conditions where one must consider the role of inappropriate secretion of antidiuretic hormone.

Discussion

Given the various facts we must now establish preferential importance among the patho-

genic factors and try to formulate a synthesis which might be useful in the treatment.

Primary Capillary Damage

The most plausible hypothesis would attribute the role of initiator to the hydro-osmotic and hydrodynamic abnormalities due to changes in the liver. From that point of view the retention of water and salt seems to be an inescapable consequent of primary capillary damage; portal hypertension, hypoalbuminemia and capillary permeability increase. They, in turn, activate the mechanisms of homeostatic control: namely, hyperaldosteronism with increased tubular reabsorption of sodium and water. This, however, does not always serve to block further aldosterone activity because water and sodium disappear rapidly from the vascular compartment and accumulate in the ascites. Moreover, the effective (arterial) circulating volume remains depressed. Circulatory abnormalities are compatible with this concept, and we have seen that together with the increased blood volume we have a diminution of arterial blood and a tendency to hypotension, parallel developments in subjects with arteriovenous fistula, where we also have a diminution of effective (arterial) circulating volume, trigger aldosteronism and sodium retention too.

Angiotensin

Nevertheless, at present one incriminates a similar but more specifically renal mechanism of secondary hyperaldosteronism; renal ischemia would be the initial event, which in turn would stimulate hyperactivity of the juxtaglomerular apparatus and hypersecretion of renin. This in turn would lead to increased production of angiotensin.[27]

Present concepts hold that in normal persons angiotensin stimulates aldosterone production selectively; in other words, a renal-adrenal regulatory mechanism of sodium balance is accepted. Diminished perfusion of the kidney releases hypersecretion of renin; this in turn releases angiotensin, and the latter stimulates aldosterone secretion. Aldosterone leads to sodium retention, which in turn restores renal perfusion and suppresses release of renin.

One could conceive that this course of events might be enhanced in hydropic cirrhosis if there actually existed renal ischemia. This seems to be the opinion of certain authors[39] who have observed a marked diminution of effective renal blood flow and of the renal fraction of the cardiac output after the advent of ascites. These renal hemodynamic abnormalities, however, are at their maximum during the stage of terminal renal insufficiency, where we have an increase of renal vascular resistance, due to vasoconstriction of the afferent arterioles of the glomeruli,[1] and, in this stage, we can also find indirect arguments in favor of an increased circulation of angiotensin.[28] However, we should not forget that during an earlier stage, namely, during the main period of the development of hydropic cirrhosis, numerous authors did not succeed in demonstrating frank renal hemodynamic abnormalities. Laragh[27,28] believes that they exist but that they elude our experimental methods. Shear proposed another hypothetic explanation: intrarenal shunts, leading to increased blood flow, so that our measurements indicating an apparently normal renal blood flow actually indicated a deficient effective flow.

The proponents of renal ischemia and subsequent stimulation of the renin angiotensin system also encounter other difficulties: for instance, why does administration of exogenous angiotensin to hydropic cirrhotics usually induce a heavy natruresis?[28]

Hyperaldosteronism

But all that does not change or deny the reality of secondary aldosteronism which, as stated, does not depend solely on renal ischemia but more generally on the effective (arterial) volume of the general circulation which is maintained by volume receptors.

This hyperaldosteronism, the role of which is all-important in the development and persistence of the hydropic syndrome of cirrhosis, reaches its highest levels in the terminal episode, in the presence of renal ischemia, whereas edema and ascites do not. But the practical importance of the aldosterone mechanism becomes irrelevant at that stage, where glomerular failure is a sufficient cause for total water and sodium reabsorption.

Let us finally remember that secondary hy-

peraldosteronism is not the only hormonal abnormality of hydropic cirrhosis and that the role of inappropriate secretion of antidiuretic hormone should not be neglected, even if its mechanism remains unexplained.[2]

All of these theoretical considerations have practical therapeutic applications.[19a]

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9-42. May be secured from the author or the reprints.

Chiari's Syndrome

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This syndrome is characterized by the presence of thrombosis of the hepatic vein or of one of its branches, with hepatomegaly, evidence of collateral circulation, and ascites. It occurs most often in young adults and somewhat more commonly in males.

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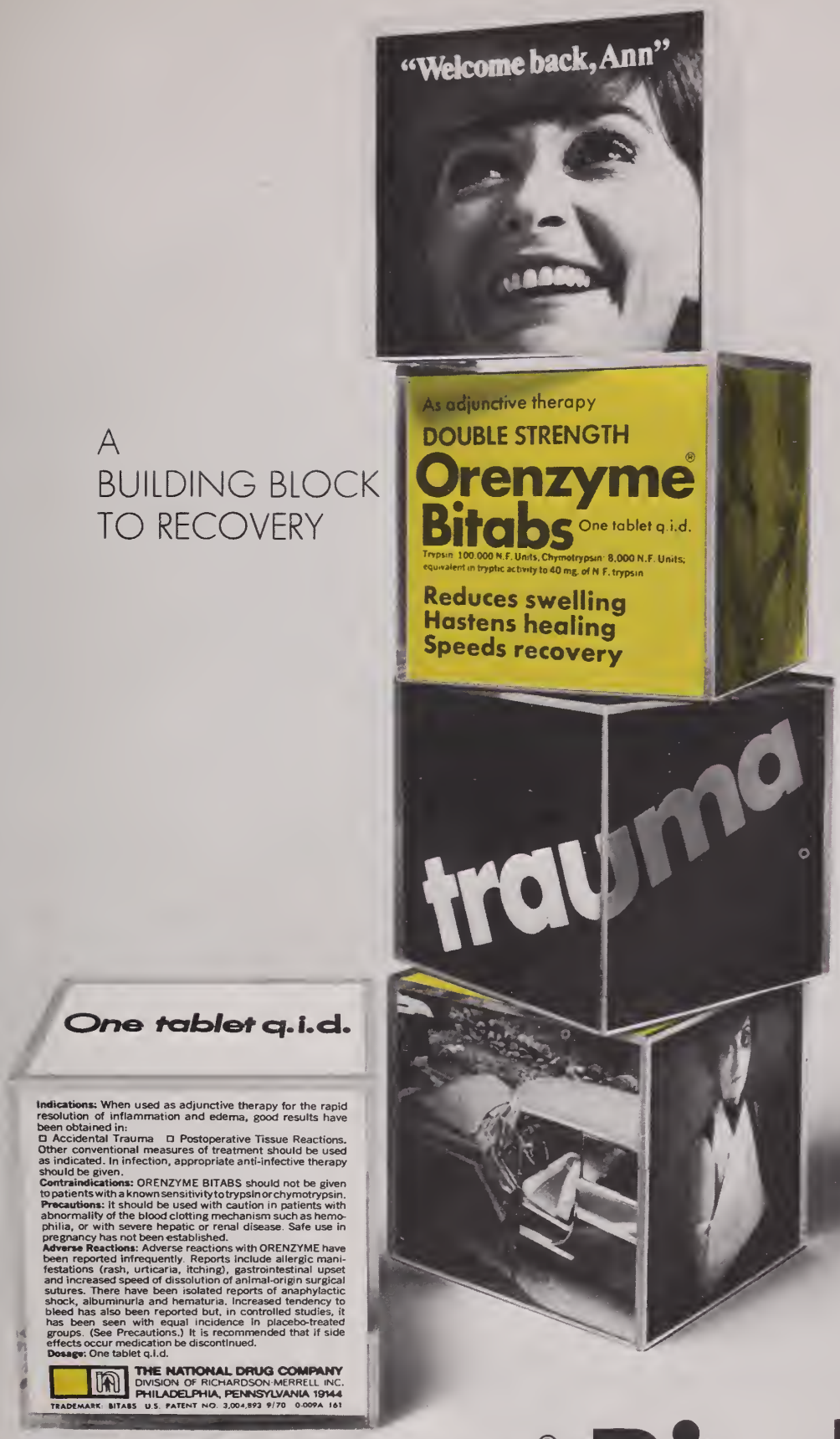
The chronic stage of the syndrome may continue for a few months, death usually occurring from hepatic coma. When hepatic vein thrombosis occurs suddenly, death may ensue within a few days.

Reference: Durham's "Encyclopedia of Medical Syndromes", Hoeber, Inc.

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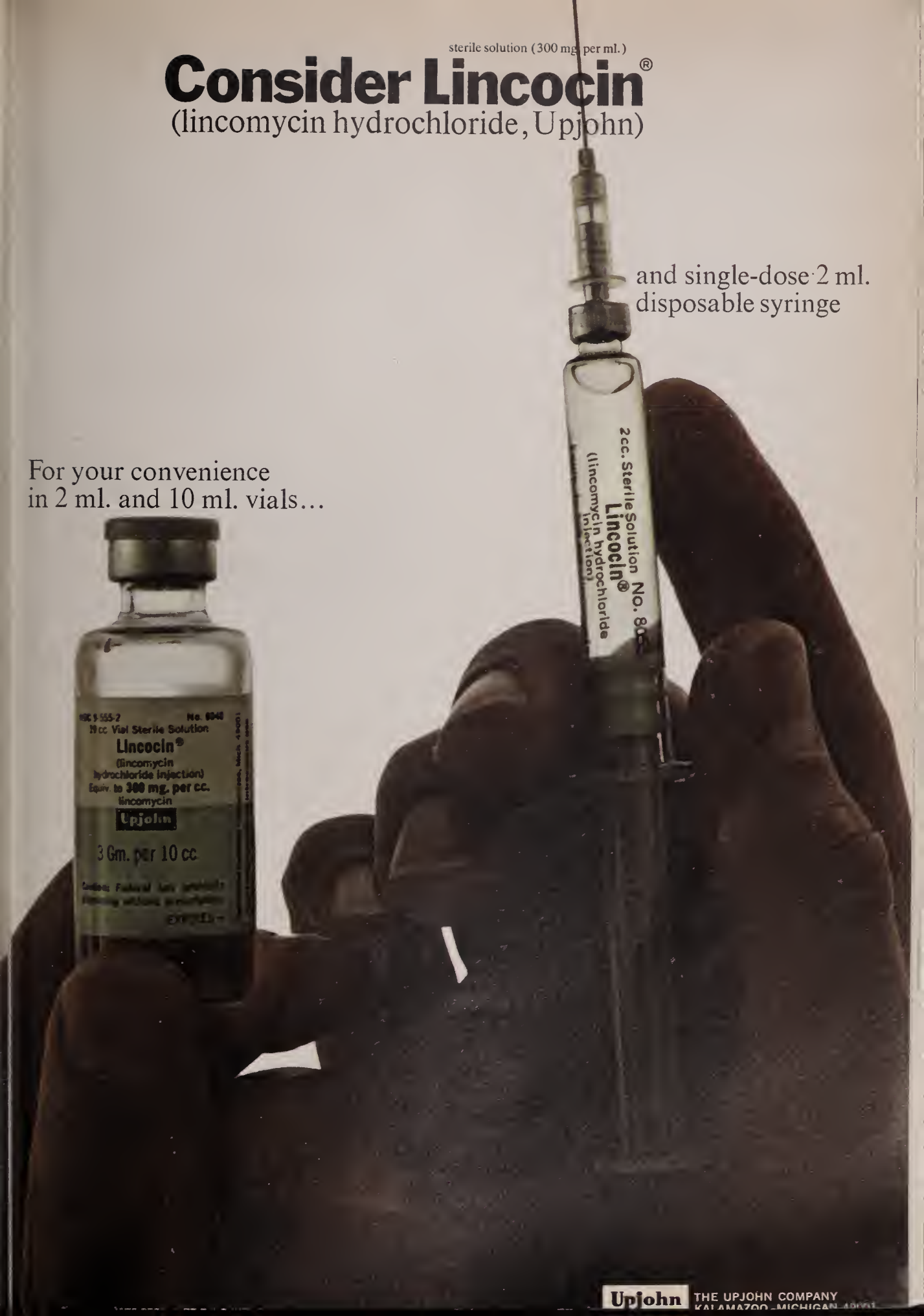
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2. Cotzias, G. C.: *J.A.M.A., 210*:1255, 1969.

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1. Duvoisin, R. C., *et al.*: *Trans. Amer. Neurol. Assoc., 94*: 81, 1969.
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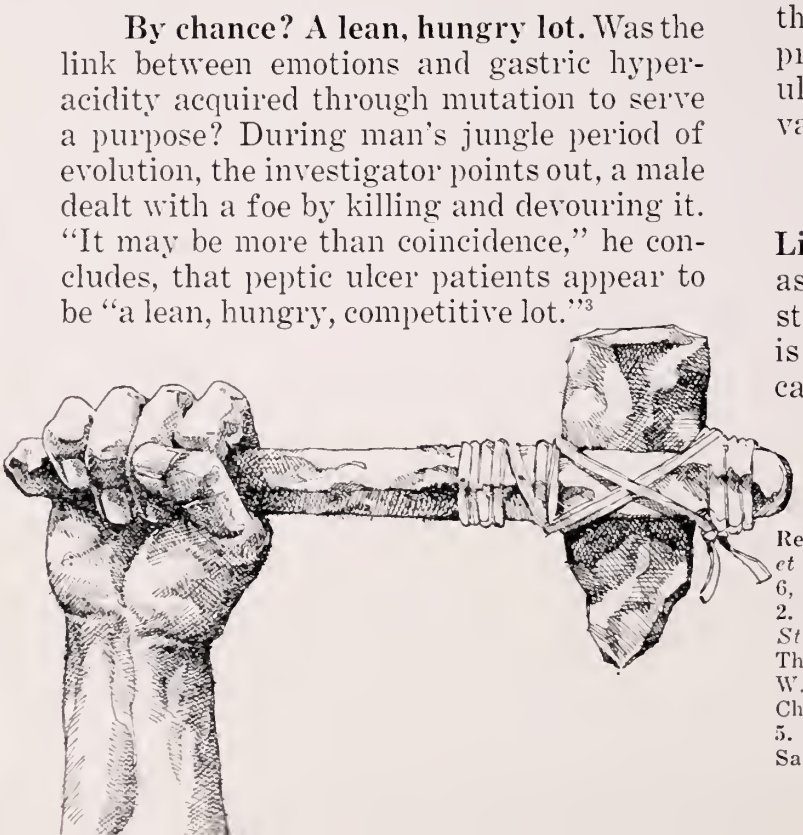
IF MORE MEN CRIE



At least seventy-five out of one hundred adults with duodenal ulcers are men.[1] Why? It may be significant that duodenal ulcer patients tend to crave recognition and are "especially vulnerable to threats to their manly assertive independence."[2]

Hypersecretion—an atavistic response. Stewart Wolf, who, with Harold G. Wolff, studied the personalities of duodenal ulcer patients, wonders if masculine competitiveness is related to "an atavistic urge to devour an adversary." It is striking, he reports, that an accentuation of gastric acid secretion and motility can be "induced in ulcer patients by discussions that arouse feelings of inadequacy, frustration and resentment."[2]

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Big boys don't cry. If more men
maybe fewer would wind up with du
ulcers. But men will be men—the sum t
their genes and wha
are taught. Schott
observes that w
mother admonish
son who has hurt hi
that big boys don't c
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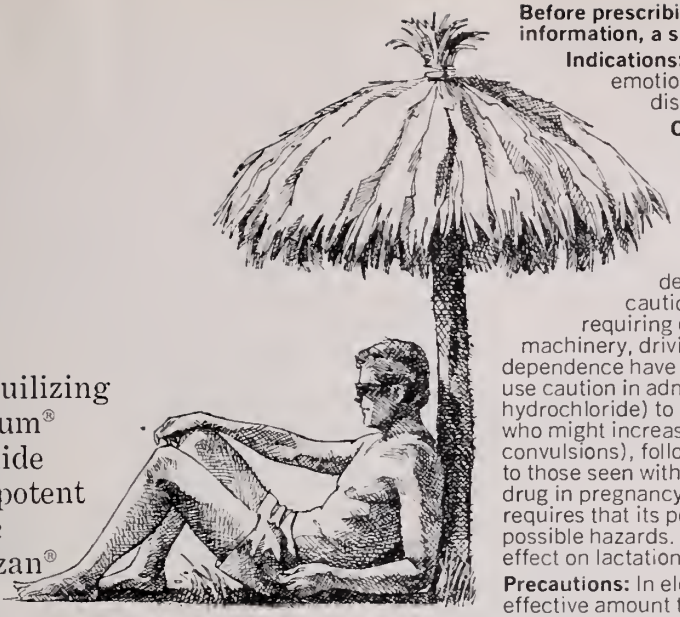


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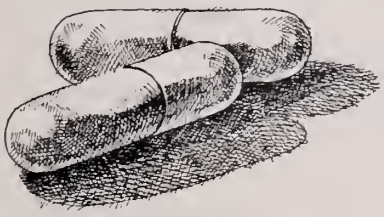
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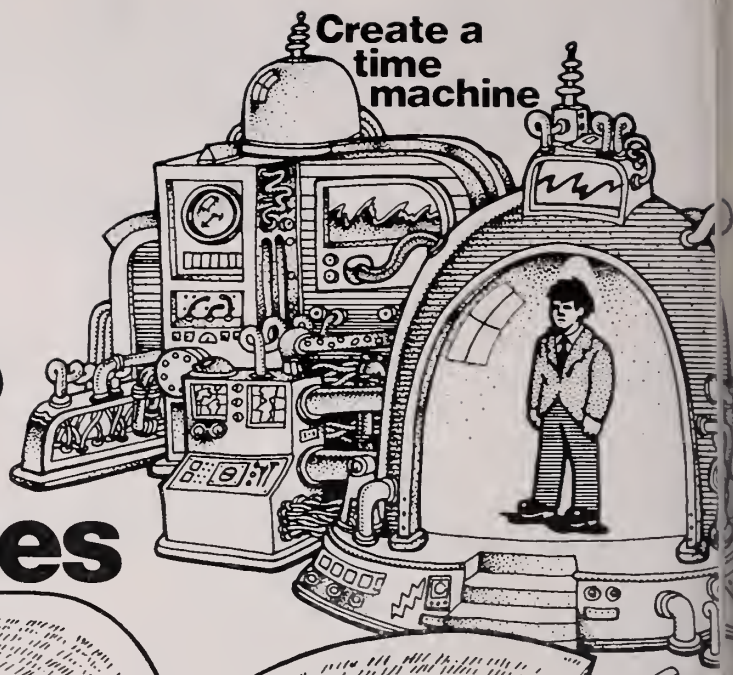
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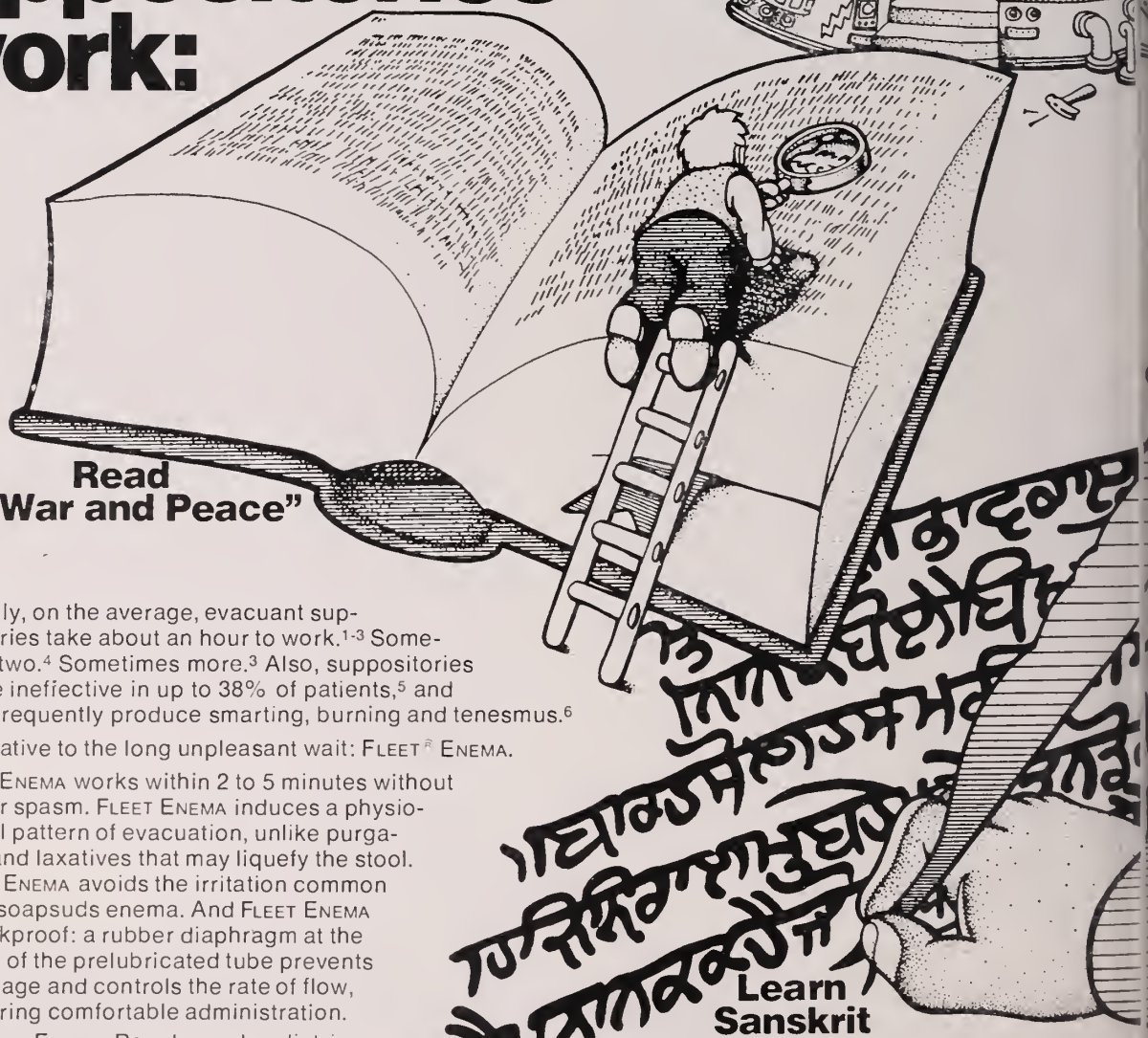
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CONTRAINDICATIONS: Patients with known hypersensitivity to the drug.

WARNINGS: Caution patients about combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle shortly after ingesting the drug.

Physical and Psychological Dependence: Physical and psychological dependence rarely reported. If withdrawal symptoms do occur they may resemble those associated with withdrawal of barbiturates and should be treated in the same fashion. Use caution in administering to individuals known to be addiction-prone or those whose history suggests they may increase the dosage on their own initiative. Repeat prescriptions should be under adequate medical supervision.

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President's Letter

Maternal Mortality Rate

SINCE THE FOUNDING of the Minnesota Obstetrical and Gynecological Society in 1936, the Minnesota Maternal Mortality Rate has dropped from over 400 to about 14 per 100,000 live births—near an irreducible minimum. Credit for this spectacular achievement is due in part to the leadership provided by the Society, to improvements in hospital and medical care generally, and perhaps especially to the general practitioners of the state who have delivered most of the obstetric care in this period.

Comparable improvement in the perinatal mortality rate has not been achieved, and little is known of maternal and perinatal morbidity rates. Available information suggests that they are high and that reductions could be attained by the application of newer techniques and principles of care. For example, emphasis in prenatal care should be changed from one of performing a prescribed set of routine checks to one of patient education in such areas as nutrition, general health, and family planning (using this term in the broadest sense). The "high-risk" pregnant patient needs to be recognized and given special prenatal attention, as well as intensive care during labor and delivery, including such things as continuous electronic monitoring of the fetal heart rate and the intensity and frequency of uterine contractions. An indispensable supplement to intensive labor and delivery care is a well-staffed and well-equipped neonatal intensive care unit.

There is widespread and well-founded concern that an inadequate number of physicians, poorly distributed, together with high costs of special facilities inefficiently used, may combine to restrict the future application of advances in maternal and perinatal care generally in the state. Two approaches to a solution suggest themselves. One is to consolidate small Obstetric Services into units large enough to justify adequate staff and facilities, concentrating "high-risk" patients into units especially designed and staffed for their care. The second approach is to train more personnel for obstetric care delivery. More physicians are now being trained, and changes in medical school curricula and the development of Family Practice as a specialty may increase the number who are interested in obstetrics. The use of non-physician associates is another area of great potential. It has already been clearly established that non-physicians properly trained and supervised can do an excellent job in patient education and counseling and in providing prenatal care, care during labor, delivery, and the puerperium, and interconceptional care for the normal patient.

A concentration of Obstetric Services and the utilization of non-physician health personnel in the delivery of care will mean major changes from tradition for both physician and patient. However, these do not seem incompatible with other profound changes in health care delivery which appear inevitable in the future.

Donald W. Freeman, M.D.
President
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Os Calcis Fractures*

An Analysis of 37

JAMES R. GAGE, M.D.† and ROBERT PREMER, M.D.‡

In 1916, COTTON AND HENDERSON[3] stated, "Ordinarily speaking, the man who breaks his heel is done so far as his industrial future is concerned. . . . Conservative treatment gives incredibly bad results." When one looks at the results of the type of conservative treatment which has been employed for this injury at Hennepin County General Hospital in the past 10 years, one gets the feeling that the statement of Cotton and Henderson may be close to the truth. It was to clarify the issue of conservative versus operative treatment in calcaneal fractures that this study was undertaken.

The injury is usually produced by a fall from a height. The fracture represents about 60 percent of all major tarsal injuries, Roughly 10 percent of all calcaneal fractures are associated with fractures of the spine, and 26 percent are associated with another major extremity injury.

Types of Fracture

The fracture has been subjected to a number of classifications. From the points of view of understanding the mechanism of injury and for prognostication, the methods of Watson-Jones[16] or Essex-Lopresti[4] are perhaps the best. In our series we have used the classification of Watson-Jones, who divides fractures of the os calcis into seven types.

Type I is a vertical fracture of the tuberosity (Figure 1). It is usually produced by a fall on a dorsiflexed foot with the heel in valgus.

Type II (Figure 2) is a horizontal fracture

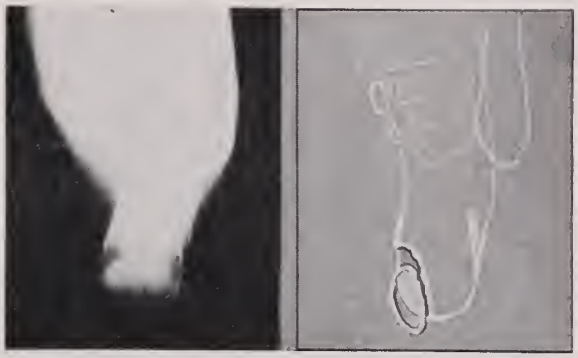


Fig. 1—Type I—Vertical Fx of the tuberosity. Etiology: shearing force; usually by falling with heel in valgus.

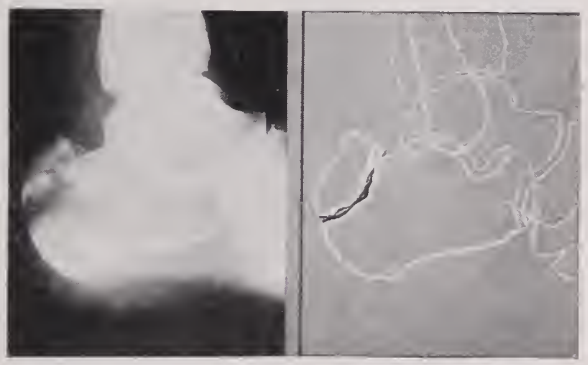


Fig. 2—Type II—Horizontal Fx of the tuberosity. Etiology: so-called "beak-fx" is apparently a variant of avulsion fx in patient with anomalous insertion of triceps surae.



Fig. 3— Type III—Fx of the sustentaculum tali. Etiology: produced by force applied to the medial side of the foot while the heel is in valgus.

*Read at the Annual Orthopedic and Fracture Seminar of the Hennepin County General Hospital, Minneapolis, Minnesota, November 8, 1969.

†Orthopedic and Fracture Divisions, Hennepin County General Hospital, Minneapolis, Minnesota.

‡Chief, Orthopedic Division, Veterans Administration Hospital, Minneapolis, Minnesota.

of the tuberosity. Protheroe[11] has recently shown that this is probably always an avulsion fracture of the triceps sura.

Type III (Figure 3) is referred to as an isolated fracture of the sustentaculum tali, although this is probably a misnomer as it usually involves a portion of the anterior process as well.

Type IV (Figure 4) is a fracture of the anterior process. It usually occurs when the foot is forced into maximum dorsiflexion. Widen[15] feels that this fracture is probably caused by avulsion of the ligamentum bifurcatum since it usually involves only the anterior superior corner of the anterior process. This fracture should always be looked for when a patient has pain in the midtarsal joints after trauma, as it will cause permanent disability if not treated.

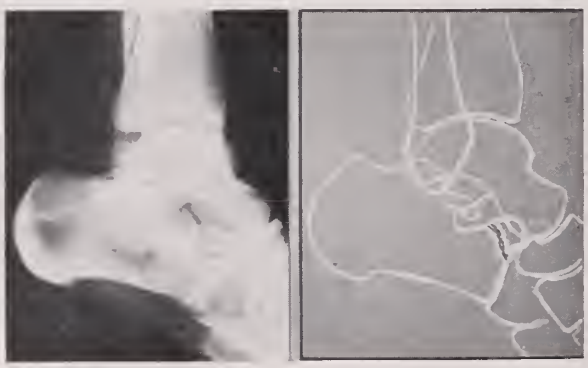


Fig. 4—Type IV—Fx of the anterior end of the calcaneum (into calcaneal-cuboid joint). Etiology: forcible twisting of foot.

Types V through VII (Figures 5-7) are fractures of the body of the os calcis. They are usually produced by a fall with the heel in neutral or valgus. In all three types the os calcis is divided into a superior-medial and an inferior-lateral piece as shown below. In the Type V fracture this fracture line does not violate the subtalar joint. In Type VI the subtalar joint is entered and there is displacement of the lateral part of the articular surface. In Type VII a secondary fracture line develops through the inferior-lateral fragment, dividing it in two. The piece thus separated is driven down into the soft cancellous bone. This can also be seen in the diagram below. When this occurs the lateral wall of the os calcis explodes outward, thus creating the disabling features of this fracture, which include disruption of the subtalar joint, heel broadening, impingement of the peroneal tendons, rocker bottom calcaneus, varus or valgus deformity of the heel, and damage to soft tissue septa.

Mechanism

Watson-Jones Types I-IV do not violate the subtalar joint. These extra-articular fractures constitute about 25 to 30 percent of all fractures of the os calcis and usually occur in younger individuals. Their prognosis is generally favorable. In a strict sense the Type V

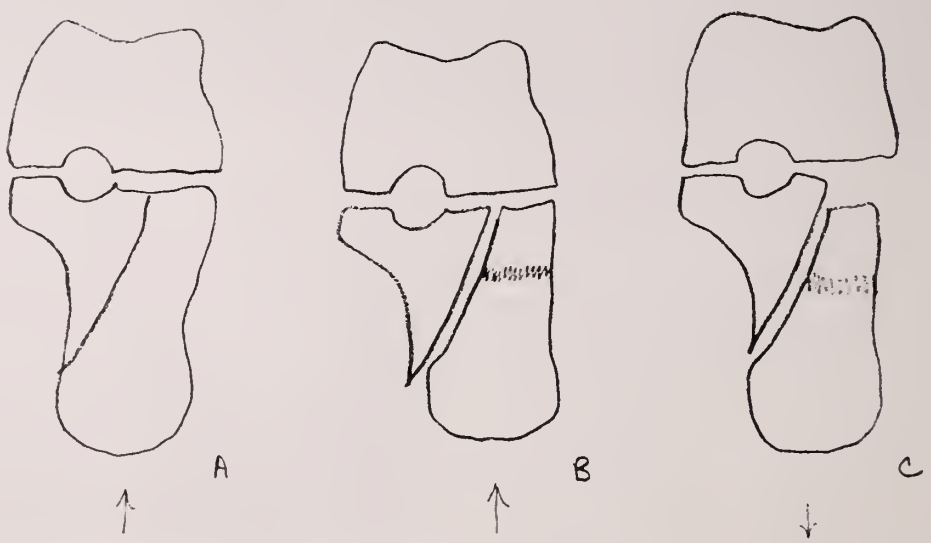


Diagram showing the mechanism of injury in intrabody fractures of the os calcis (after Palmer[12]). A and B show continuing compression from below; C shows rebound of the fragment when the compression force ceases.

fracture is intra-articular; but since the joint surfaces are not involved by the fracture it also carries a good prognosis.

Treatment of Intra-articular Fractures

It is with fractures of the body of the calcaneus which enter the subtalar joint (W-J VI and VII) that there is residual disability in a high percentage of cases, and it is with the treatment of these fractures that we are primarily concerned.

Treatment of the intra-articular group can be broken down into four major categories which are conservative, i.e., non-surgical: treatment with or without reduction, reduction using percutaneous pins, open reduction, and open reduction with arthrodesis of one or more joints.

Non-surgical

In the past, non-surgical treatment has usually consisted of plaster immobilization without reduction, often in a walking cast. Results of this type of treatment have been less than satisfactory. In the past few years the tendency has been towards immediate active motion with non-weight bearing for six to eight weeks. Thören[14] has treated a series of 113

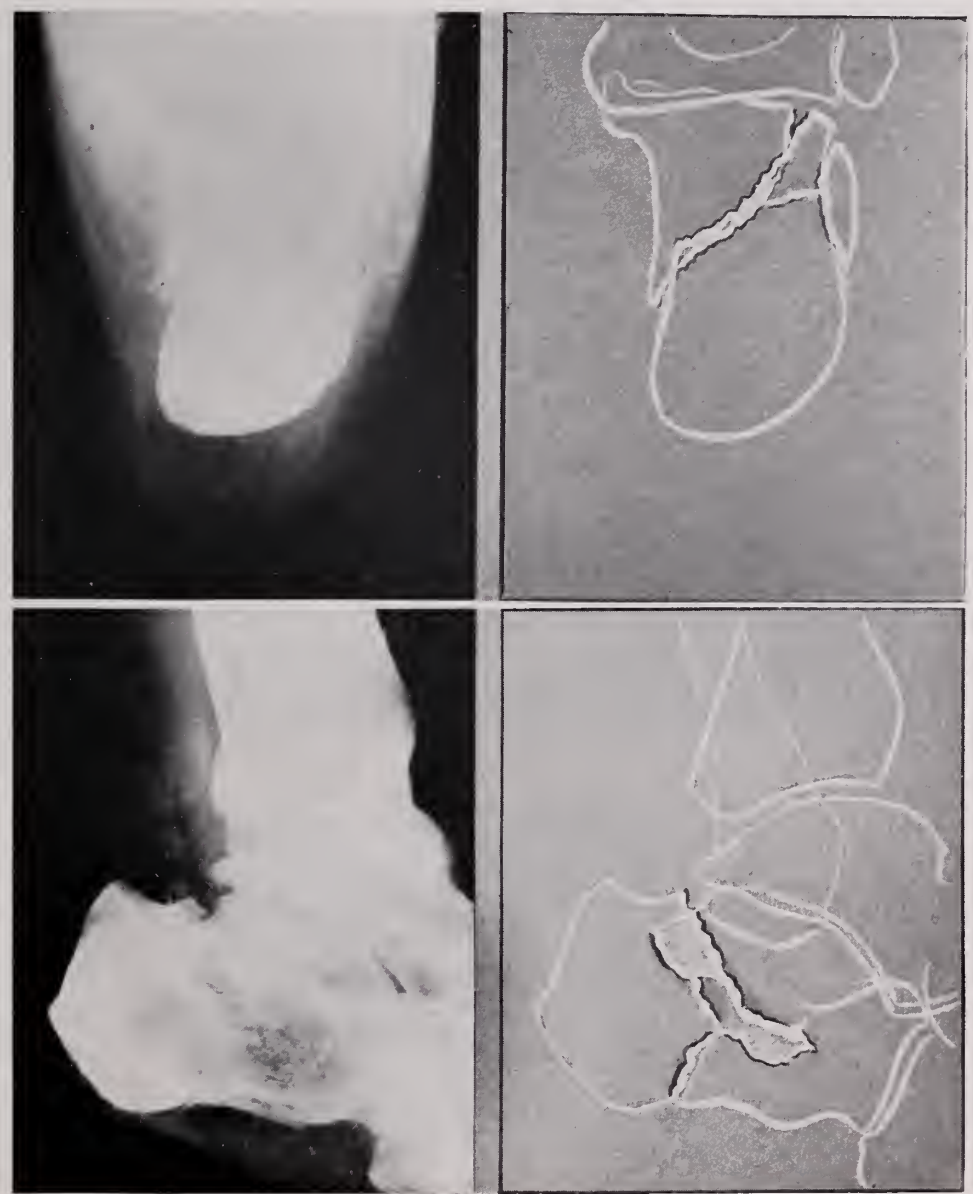


Fig. 5(a) and (b)—Type V—Fx adjacent but not entering subtalar joint. Etiology: vertical compression.



Fig 6(a) and (b)—Type VI—Fx with displacement of the lateral half of the subtalar joint. Etiology: vertical compression, probably with heel in valgus.

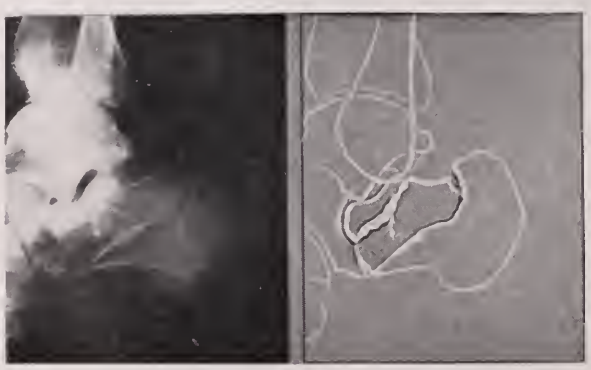


Fig. 7—Type VII—Fx with central crushing of the whole subtalar joint and sometimes also the calcaneal-cuboid joint. Etiology: vertical compression.

cases of intra-articular fractures in this manner and reported 65 percent good results. Cotton and Henderson[3] devised a method of closed manipulation in 1916 which is still in use today. Aitken[1] reports 75 percent good results by this method. However, he gives no details of the size of his series or his method of evaluation.

Pins with Traction

Percutaneous pins with traction for reduction was pioneered by Böhler.[2] He treated 250 fractures of the calcaneus between 1926 and 1935 by this method and was able to follow 195 of his patients. Of these, 147 had resumed their previous trades, 41 had different jobs, and only seven were not working.

Essex-Lopresti[4] either manipulated the fracture with percutaneous pins or combined open reduction and percutaneous manipulation depending on the specific type of fracture. He reported on 180 intra-articular fractures and was able to follow 173 of these, with 65 percent good and 30 percent fair results over-all. In those persons under 50 in whom he was able to successfully reduce the fracture, he had 80 percent good and 18 percent fair results as compared to 63 percent good and 35 percent fair results in patients under age 50 whom he treated conservatively with active motion and without reduction. With open reduction after age 50, however, his percentage of good results dropped to 40 percent even with successful reduction.

Open Reduction

The method of open reduction which is currently in vogue was described by Palmer[12] in 1948. The largest series of open reductions is reported by Widen,[15] who trained under Palmer. He performed 69 open reductions and was able to follow 56 of them. He reported 66 percent good and 20 percent fair results. It should be noted, however, that there were 142 cases in his series and that only the more severe fractures were opened.

Arthrodesis

Arthrodesis may be only of the subtalar joint, or it may be a triple arthrodesis. Moberg[10] performed triple arthrodeses in the 37 most severe fractures of the 98 in his series. The operation was performed at six weeks after first securing reduction with pins and traction ad modum Böhler. He reported generally good results.

Hall[5] does an open reduction by the Palmer method with primary subtalar arthrodesis and reports 74.1 percent good and 19.3 percent fair results in a series of 44 fractures.

Table 1, reproduced below, was taken from the article by Lance et al.[6] and summarizes the factors found in unsatisfactory results in their series of 227 intra-articular fractures of the os calsis:

TABLE I

Comparison of Satisfactory and Unsatisfactory Results—Factors Occurring More Often in Unsatisfactory Results

Factor	Unsatisfactory Results
Compensation	60%
Open Fracture	2 of 3
Severe Comminution	66%
Pin Traction Treatment	71%
Clinical Deformity	
Valgus	61%
Varus	67%
Lateral Exostosis	88%
Loss of Heel Pad	100%
Subtalar Motion 50% or Less	75%
Diminished Motion of Ankle or Tarsus	65%
Complication (infection, etc.)	94%

When Böhler's angle was 15°, the results were on the whole satisfactory; in the unsatisfactory cases, the angle averaged 6°.

Thören[14] statistically correlated deformities and end result and found that the displacement of the posterior facet of the subtalar joint correlated highest with the end result, and that Böhler's tuber-joint angle correlated next highest.

Types of Fracture

Os calcis fractures treated at Hennepin County General Hospital during the period 1960 to 1968 were reviewed. Sixty-two patients with this diagnosis were admitted during this period, although many did not choose to remain at General Hospital for their treatment. The fractures were classified by using the original x-rays when they were available. In some cases the radiologists' reports were adequate to classify the fractures when the

x-rays were not available. Our breakdown into types of fractures is as follows:

Type	Number	Percent of Total
I	2	3.0%
II	5	7.7%
III	0	0.0%
IV	1	1.5%
V	3	4.6%
VI	8	12.3%
VII	38	58.5%
Unclassified	6	9.2%

A questionnaire was sent to each of the patients. We received 18 replies, 17 from patients and one stating the patient was deceased. Sixteen letters were returned because the patient had left no forwarding address. There were two patients that were still being followed in clinic. Finally, there were 18 patients who did not respond to the questionnaire but who had been followed for six months or more in clinic and had sufficient data on their charts to allow us to judge what their end result was at the time they were last seen. Our series, then, is made up of 37 cases. Two patients had bilateral fractures.

We graded our patients functionally as: good, those who had no symptoms or whose symptoms were mild enough not to be limiting or disabling; fair, those who had pain and/or edema sufficient to impose some limitation on their activity; and poor, those who had marked pain and/or edema. Originally, Type VI and Type VII fractures were separated, but since there appeared to be no significant difference between them, we decided to consider them as one group. Fractures which did not violate the subtalar joint surfaces (W-J Types I-V) were also considered together.

In evaluating our end results we were able to consider the patients' ages, the length of follow-up, the tuber-joint angles, and in some cases whether or not the fracture extended into the calcaneal-cuboid joint. Other variables such as heel valgus, heel width, etc. could not be evaluated without a follow-up examination. The method of treatment, of course, was also considered. The following is a summary of the extra-articular fractures of our series:

Fractures Not Involving the S-T Joint (W-J Types I-V)
(seven fractures, mean patient age 39)

Treatment	Results		
	Good	Fair	Poor
Dressing or Plaster	4	2	0
Screw Fixation of Tuberosity	1	0	0

Results

We had 71 percent good and 29 percent fair results in this group of fractures. One of the seven fractures in the group was a Type V fracture and this patient had a good result.

TABLE 2
Fractures Involving the Subtalar Joint (W-J Types VI & VII)

Treatment	Results			Mean Age
	Good	Fair	Poor	
Conservative (dressing or plaster)	6	7	10	53
Closed Manipulation	3	0	0	47
Percutaneous Pins	0	0	1	42
Open Reduction	0	1	1	36
Primary Arthrodesis	0	0	1	44
Total Results (30 cases)	9	8	13	

Our intra-articular fractures at Hennepin County General Hospital showed the following results: 30 percent good, 27 percent fair, and 43 percent poor. There were two other fractures, one with a fair and one with a poor result, which I was unable to classify because the x-rays were not available.

Several things are of interest when looking at the data. In the patients with good results, Böhler's tuber-joint angle averages 17° compared to 5° in the group with the poor results. Secondly, the good results have the longest period of follow-up; it has been a general observation that this injury is associated with a long period of slow improvement which may last as long as two years. Thirdly, the average age of the patients with fractures of the body of the calcaneus is about 50 compared to a mean age of 39 for patients with extra-articular injuries. This has been noted by Widen,[15]

Essex-Lopresti,[4] and others. Finally, in our group we have three patients with excellent results following closed manipulation. We have no explanation for this, and the number is not statistically significant.

Conservative vs. Operative Treatment

One of the best series of os calcis fractures in a general hospital is that of Lindsay and Dewar,[7] who traveled over 5,000 miles in order to personally examine patients. There were 390 patients in their series, 147 of whom were followed and compared as to their end results. In fractures of the subtalar joint with displacement, 76 percent of the conservatively treated and 60 percent of the operatively treated group had good results. Dividing the conservatively treated group into manipulated and non-manipulated subgroups, they found that the former subgroup had 72 percent and the latter 81 percent good results.

The over-all results of our series (30 percent good, 27 percent fair, and 43 percent poor) are not good. The series is primarily one of conservatively treated fractures without reduction. Most of our patients were treated with compressive dressings and elevation for about one week and then were casted for six or more weeks, often in a walking cast. Several questions can be raised as to why our *results* compared so badly with both the conservative and the operative series in the literature.

Perhaps in discarding the short-term follow-ups, we eliminated many good results since problem cases would have to be followed longer in the clinic? Reviewing the fractures that were discarded with follow-up time of between three and six months, we add two good, one fair, and two poor results to the series. Thus we would not materially up-grade the series by adding these patients.

Immobilization

Perhaps iatrogenic stiffness is added to an already difficult problem by using cast immobilization. It has been demonstrated in the literature by both Thören and Essex-Lopresti that one can attain about 65 percent good results by treating all of these injuries with non-weight bearing and active motion. In both of these large series there has been no problem with further loss of position so long as weight-bearing was not permitted; and since the os calcis is a cancellous bone, non-union is not a problem. In many of our poor results the cast was left on for an excessively long period, sometimes for as long as 12 weeks. Thus we may have added joint fibrosis which active motion might have prevented.

Weight-Bearing

Finally, perhaps weight-bearing should not be allowed even with the protection of plaster. Lance[6] and others warn against further loss of position with early weight-bearing. In our series, we have one poor result in a patient who was held in plaster for four weeks and then taken out and allowed to weight bear immediately. Her tuber-joint angle settled from about 20° to 0°, but this did not occur until plaster was discontinued.

Conclusions

The most consistent results, especially for one who has not had a great deal of surgical experience with this fracture, could be obtained by using active motion and non-weight-bearing for at least eight weeks. The methods of Palmer and Essex-Lopresti require surgical talent which is learned by repeatedly performing the procedure. However, this is not sufficient reason to abandon operative treatment. For in the younger patient with a displaced fracture through the subtalar joint, Palmer,[12] Essex-Lopresti,[4] Widen,[15] and Maxfield[8] have all shown that surgical results are better, even though convalescence is somewhat longer. Therefore, we would urge that cast treatment be abandoned in favor of operative reduction in the younger patient and treatment by active motion with non-weight-bearing for eight weeks in older individuals.

Discussion

Thomas H. Comfort, M.D.*

The extra-articular fractures did well independent of their treatment. This is a generally applicable conclusion; however, the crush fracture of the anterior part of the os calcis at the calcaneal cuboid joint does not routinely do well. The type IV fractures of the anterior pro-

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cess of the os calcis are actually very common and, I am sure, were treated as outpatient fractures and, therefore, not included in his series. However, the general experience has been that these do not do well unless they are protected in a cast for a six-week period.

The subtalar fractures are particularly difficult to evaluate since the principles of treatment are not defined. We all have patients who complain of continual aching in the heel, cannot walk on their toes, and are unable to return to work. But are the bad results due to soft tissue, joint or bony injury? As Dr. Gage reviewed the literature, two thirds to three quarters of the patients receive good results with the conservative reconstruction or fusion therapies; therefore, it is not clear whether our primary goal of treatment should be early motion, avoidance of swelling, and progressive physical therapy emphasizing the restoration of the soft tissue injury; or reconstruction of joint alignment and, if this fails, early arthrodesis to treat the arthrosis of the subtalar joint; or realignment of the arch of the foot if avoiding the varus and valgus deformities and restoring the length of the tendon Achilles are of prime importance. If you neglect all of these factors, with early weight-bearing, the results are poor. In the conservative therapy group there are 10 of 23 poor results because of persistent pain. Other analyses have shown that poor results correlate with a poor Böhler's angle or with varus or valgus deformities of the feet. I would like to emphasize that conservative treatment should not be confused with no treatment and that sufficient protection be given to the fragmented bone so that it is not allowed to further flatten in a position of increased deformity.

Selected cases can be treated by percutaneous pins with open reconstructive procedure, with bone graft, or with internal fixation with staples or wires. In order to avoid disaster, the fracture must be carefully analyzed before treatment so that a nontraumatic approach can be made which will effectively stabilize the fracture. Skin healing is poor in this area and infected operative wounds have caused severe disasters in attempts to improve os calcis treatment.

Two series have shown that early triple arthrodesis is not a good answer to treatment of os calcis fracture. Moberg was unable to improve on the return-to-work record or the post-fracture pain due to more conservative methods. Dewar and Lindsay analyzed 390 histories from the Workmen's Compensation cases of Ontario and found that of the 20 who had surgical arthrodesis 70% continued to have poor results. Therefore I think triple arthrodesis should be retained for those cases with rocker bottom foot or severe varus or valgus deformity, rather than employed as a primary mode of treatment.

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Looking at Others

Psychiatrists say we are all a little strange in our behavior. Another way of saying this is: "I'm original. You're eccentric. He's nuts."*

*The Speaker's Handbook of Humor, Maxwell Droke.

Splenic Rupture

A Review of 114 Cases

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CLAUDE R. HITCHCOCK, M.D., Ph.D.‡

CELSUS FIRST REPORTED a case of splenic rupture in the 15th century A.D. By 1923 there were more than 500 cases reported and more than 1,000 by 1950.[6] Since then the literature on splenectomy and splenic rupture has mushroomed. It was noted that during the year 1969, 50 splenectomies were performed at the Hennepin County General Hospital for all indications. Since rupture of the spleen is usually a surgical emergency, it was decided to review our experience with splenectomies over the last several years to evaluate our incidence and indications for splenectomy, the clinical picture of splenic rupture, and our overall surgical results with splenectomy. Following a brief discussion of the indications for and incidence of splenectomy, this article will be limited to a discussion only of the ruptured spleen.

Indications for Splenectomy

During the 11 years between January 1, 1959 and December 31, 1969, there were 254 splenectomies done at the Hennepin County General Hospital. Table I lists the indications for splenectomy and the number of patients included in each group.

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TABLE I
Indications for Splenectomy

Total Splenectomies		254
Missing Charts	10	
Total Reviewed		244
Traumatic Rupture	109 (44.7%)	
Incidental	61 (25.0%)	
Spontaneous Rupture	5 (2.1%)	
Part of Operation	21 (8.6%)	
Splenic Disease	17 (6.9%)	
Renal Program	31 (12.7%)	

Incidence

During the period of the study there were 16,875 patients admitted to the general surgical service at Hennepin County General Hospital with 114 (0.7%) undergoing an emergency splenectomy. During this 11-year period there was a general increase in the number of admissions per year to the surgical service as well as a relatively greater increase in the number and incidence of splenectomies performed each year (Table 2). Splenectomies done for traumatic rupture and for the hemodialysis program accounted for most of this increase, while the number of incidental splenectomies increased only slightly. Splenectomies for other indications remained relatively constant throughout this period.

TABLE 2
Incidence of Splenectomy for Trauma

Year	Admissions	No. Done	Incidence
1959	1057	4	0.4%
1960	1130	3	0.3
1961	1263	3	0.2
1962	1356	8	0.6
1963	2063	5	0.2
1964	1519	15	1.0
1965	1671	7	0.4
1966	1757	12	0.7
1967	1485	13	0.9
1968	1805	21	1.2
1969	1769	18	1.0
Total	16857	109	0.6%

Note: There were five patients originally diagnosed as having spontaneous rupture who are included in the total number (114) who underwent emergency splenectomy.

Traumatic Rupture

One hundred nine patients sustained a traumatic rupture of the spleen during the 11-year period. Table 3 includes a breakdown of these patients into the various categories with respect to mechanism of injury. The other blunt category includes beatings, falls, hits by

a train, and one helicopter accident. Patients who suffered other injuries amounting to more than minor lacerations or bruises were considered to have multiple injuries.

Age

The age distribution for the isolated and for the multiple-injury groups is similar (Table 4). The peak incidence for automotive and cycle injuries was found in the second and third decades, while pedestrians were either younger or older. Other blunt injuries were evenly distributed throughout the first through the sixth decades of life, while the penetrating injuries were concentrated in the second through the fourth decades.

Sex

The overall sex ratio male to female was 1.7 to 1 (Table 5).

Associated Injuries

The associated injuries among the patients with multiple injuries were many and varied (Table 6). Patients with penetrating injuries had no associated injuries outside of the chest and abdomen.

Physical Examination and Diagnosis

Shock

Shock occurred in 69 (79%) of the patients with multiple injuries and in 20 (91%) with isolated splenic ruptures. While shock occurred more frequently in patients with isolated injury, it was usually less severe.

Abdominal Findings

Other common signs and symptoms of splenic rupture included abdominal pain, tenderness, and guarding or rebound either diffuse or localized to the left upper quadrant. Several patients had abdominal signs localized to the right upper quadrant only, with no apparent involvement of the remainder of the abdomen. Absent or decreased bowel sounds and a tense or distended abdomen were frequently seen. Twenty-nine patients in the multiple-injury

TABLE 3
Classification of Trauma

	Auto	Cycle	Pedestrian	Other Blunt	Penetrating	Total
Multiple Injury	41	7	10	12	17	87
Isolated Injury	8	2	2	9	1	22
Total	49	9	12	21	18	109

TABLE 4
Age Distribution

Multiple Injury							Isolated Injury					
Aut	Cyc	Ped	Blu	Pen	Tot		Aut	Cyc	Ped	Blu	Pen	Tot
2	0	1	1	0	4	0-10	0	0	1	0	0	1
10	3	0	3	5	21	11-20	0	1	0	3	0	4
14	4	0	1	4	23	21-30	2	1	0	2	1	6
6	0	1	2	5	14	31-40	3	0	0	2	0	5
8	0	2	2	2	14	41-50	1	0	0	1	0	2
0	0	3	3	1	7	51-60	0	0	0	1	0	1
1	0	2	0	0	3	61-70	1	0	0	0	0	1
0	0	1	0	0	1	71-80	1	0	1	0	0	2

TABLE 5
Sex Distribution

Multiple Injury							Isolated Injury					
Aut	Cyc	Ped	Blu	Pen	Tot		Aut	Cyc	Ped	Blu	Pen	Tot
22	6	7	11	10	56	Male	2	2	1	6	1	12
19	1	3	1	7	31	Female	6	0	1	3	0	10

group (33%) had left lower rib fractures. Kehr's sign (pain referred to the left shoulder) was present in only three (3.4%) of the multiple-injury patients and in seven (33%) of the isolated injury group (Table 7).

TABLE 6
Associated Injuries

Head	Intracranial	23
	Fx. Skull	8
	Fx. Face Bones	11
Thorax	Pneumothorax	14
	Hemothorax	9
	Hemo-pneumothorax	16
	Fx. Ribs/Sternum	28
	Crush Chest	5
	Rupt. Diaphragm	16
	Contused Lung	7
	Hemomediastinum	2
	Pneumomediastinum	2
	Subq. Emphysema	2
Heart	Myocardial Injury	5
	Hemopericardium	2
	Rupt. Papillary Muscle	1
Abdomen	Liver Injury	24
	Gallbladder Injury	3
	Stomach	8
	Pancreas	13
	Bowel/Intestine	6
	Mesentery	6
	Inferior Vena Cava	1
	Adrenal	3
GU	Kidney/Ureter	21
	Bladder	3
	Urethra	1
	Retroperit. Hematoma	12
	Hematuria	6
Upper Extremity and Back	Fx. Upper Extremity	12
	Scapula	5
	Clavical	2
	Spine	1
	AC Separation	1
	Dislocated Elbow	1
	Cord Injury	1
Lower Extremity	Fx. Pelvis	16
	Hip	3
	Femur	6
	Leg/Foot	11
	Dislocated Hip	1
	Knee	2
Skin	Multiple Lac/Bruises	28
	Burns	1

Paracentesis Abdominis

Prior to 1965 four quadrant abdominal needle taps were commonly done to establish the presence of hemoperitoneum. After 1965, lavage taps using a peritoneal dialysis cannula inserted below the umbilicus were used and, if blood was not initially aspirated, one liter of dialysate was instilled through the cannula and allowed to run out by gravity as the patient was turned from side to side.

Management

Airway

Primary attention is paid to the airway; then to blood volume restoration; and finally to management of the spleen, when this is an isolated injury, or to assessing priorities to other organs in the multiple-injury patients. We have, for example, delayed splenectomy, when loss of blood volume is not of paramount importance, in preference to evacuating an acute epidural or subdural hematoma. Following the splenectomy, attention is given to the other injuries which do not have priority over the ruptured spleen.

Delayed Rupture

All patients with penetrating injuries were explored within a very few hours after the injury. Thirteen of 91 (14%) patients suffering blunt trauma had delays of from two to 21 days between the time of trauma and the onset of symptoms referable to a ruptured spleen. An additional five patients had an interval of 12 to 24 hours between the time of injury and the onset of symptoms.

Blood Replacement

In those patients with isolated injury to the spleen, blood requirements were similar in the preoperative, intra-operative, and postoperative periods, irrespective of the mechanism of injury. However, in the multiple-injury patients, those who sustained their injuries as pedestrians were found to require considerably more preoperative and intra-operative blood than the other patients of this group, thus reflecting the more extensive injuries that the pedestrian frequently sustains (Table 8).

Postoperative Care

Prophylactic antibiotics were used only sporadically, and anticoagulants were seldom used except for specific indications such as deep thrombophlebitis or pulmonary embolus.

Morbidity

Twelve of 22 (55%) patients with isolated

splenic injury and 18 of 87 (21%) with multiple injuries had no significant morbidity. The morbidity in the remaining 69 multiple-injury patients and 10 isolated injury patients is listed in Table 9. Postoperative complications were principally pneumonia, atelectasis, and urinary tract infection.

Postoperative Stay

The postoperative hospitalization for the 22 patients with isolated injuries averaged 7.9 days, whereas multiple-injury patients stayed in the hospital for an average of 25.3 days. Severity of other injuries was the significant factor determining length of hospital stay.

Mortality

Whereas there were no deaths among the patients with isolated injury, the mortality among patients with multiple injuries was 17.2% (15 patients). The causes of death are summarized in Table 10. Survival time following surgery ranged from 0 to 21 days.

Spontaneous Rupture

In addition to the 109 emergency splenectomies done for traumatic rupture, there were five done for "so-called" spontaneous rupture of the spleen. There were no distinguishing features in any of these patients and the diagnosis was made at laparotomy in each case. There was no mortality in this group.

One patient had the sudden onset of left upper quadrant pain with radiation to both shoulders while engaging in normal sexual intercourse. He was explored soon after arrival and found to have a ruptured splenic cyst. Further questioning revealed that several years prior he had been hit in the left upper quadrant while playing hockey and was hospitalized for one day with vague abdominal symptoms. Although there was no significant trauma at the time of rupture, this patient would most likely fit into the category of a late delayed rupture.

A second patient had vague abdominal pains for seven days prior to admission and the sudden onset of left upper quadrant pain the day

TABLE 7
Physical Findings and Diagnosis

Multiple Injury							Isolated Injury					
Auto	Cycl	Ped	Bl'nt	Penet	Tot'l		Auto	Cycl	Ped	Bl'nt	Penet	Tot'l
1	0	0	0	2	3	No Symptoms	0	0	0	0	0	0
34	6	10	7	12	69	Shock	8	2	2	7	1	20
5	0	1	4	0	10	Falling Hgb	1	0	0	2	0	3
5	1	0	0	0	6	Bruises on L	0	0	0	0	0	0
21	3	4	7	6	36	*	4	2	2	9	0	17
1	0	0	2	0	3	†	2	0	0	0	0	2
13	3	1	3	2	22	‡	2	1	1	3	0	7
8	1	3	1	1	14	Dist. Abdomen	0	0	0	0	0	0
1	0	0	2	0	3	Kehr's Sign	3	1	0	3	0	7
1	0	0	0	0	1	Doughy Abdom.	0	0	0	0	0	0
17	5	4	7	1	34	+ Lavage/Tap	3	1	0	5	1	10
0	1	1	0	0	2	— Lavage/Tap	1	0	0	0	0	1
8	0	1	0	0	9	+ 4 Quad. Tap	1	0	0	1	0	2
0	0	0	0	0	0	— 4 Quad. Tap	1	0	0	0	0	1
14	2	4	8	1	29	Fx. Ribs	—	—	—	—	—	—

*Diffuse or L.U.Q. Symptoms
†R.U.Q. Symptoms
‡No or Decreased Bowel Sounds

TABLE 8
Blood Replacement (C.C.'s)

		Preoperative	Operative	Postoperative
Multiple Injury	Range	0 to 9,500	0 to 18,000	0 to 39,000
	Average	1,312	2,932	1,349
Isolated Injury	Range	0 to 3,000	0 to 2,500	0 to 500
	Average	477	1,343	67

TABLE 9
Morbidity

	None	Multiple Injury 18	Isolated Injury 12
Wound	Infection	3	0
	Drain Site Infection	6	0
	Drain Site Hemorrhage	1	0
	Evisceration	1	0
CNS	Diabetes Insipidus	1	0
	Inappropriate ADH Response	1	0
	Diplopia of ? Etiology	1	0
	DTs	5	0
	Neurogenic Shock	1	0
	Emotional Disturbances	3	0
Respiratory	Pneumonia	24	2
	Atelectasis	10	3
	Aspiration Pneumonia	2	0
	Empyema	1	0
	Upper Respiratory Infection	2	0
	Spontaneous Pneumothorax	1	0
	Recurrent Pneumothorax	1	0
	Recurrent Hemothorax	1	0
	Pulmonary Congestion	2	0
	Pulmonary Embolus/ Infarct	2	0
	Fat Embolus	3	0
	Pleural Effusion	7	0
Cardiovascular	Arrest	2	0
	Ischemia	0	1
	Congestive Heart Failure	1	1
	Pericarditis	1	0
	Arrhythmia	2	1
	Transfusion Reaction	0	1
	Blood Dyscrasia	2	0
	Hypertension	1	0
	Shock	0	0
	Gram Negative Shock	2	0
	Electrolyte Imbalance	1	0
	Thrombophlebitis	3	0
GI	Upper Gastrointestinal Hemorrhage	5	0
	Ileus	1	0
	Fecal Impaction	1	0
	Obstruction	2	0
	Iatrogenic Liver Laceration	1	0
	Peritonitis	1	0
	Jaundice	2	0
	Liver Necrosis	1	0
	Ascending Cholangitis	1	0
	Hemorrhagic Pancreatitis	3	0
	Acute Inflammation of Bowel	2	0
	Subphrenic/Hepatic Abscess	8	0
	Pancreatic Fistula	4	1
	Biliary Fistula	2	0
	Peritoneal Hemorrhage	1	0
GU	Urinary Tract Infection	13	2
	Retention	0	1
	Acute Renal Failure	2	0
	Anuria	2	0
	High Output Failure	1	0
	Periurethral Abscess	1	0
	Hemorrhagic Cystitis	1	0
	Urethral Stricture	1	0
	Impotence	1	0
Other	Fever of Undetermined Origin	4	2
	Hematoma of Shoulder ? Etiology	1	0
	Drug Reaction	1	1

TABLE 10
Cause of Death

	No. of Patients
Brain or Brain Stem Injury	6
Massive Hemorrhage	3
Pulmonary Embolus	1
Cardiac Arrest	1
Hemopericardium	1
Anuria and Shock	1
Traumatic Hemorrhagic Pancreatitis	1
Massive Peritonitis	1

prior to admission. He was admitted in shock and his abdomen was explored. A ruptured spleen was found. The patient smelled of alcohol on admission and, though no history of specific trauma could be established, he was probably an alcoholic who was injured several days prior to admission. He also had active clinical tuberculosis. The spleen weighed 100 grams and had areas of caseation.

Another patient was explored because of acute abdominal symptoms and findings and had a ruptured spleen. No history of trauma could be established; however, notes in the chart suggest a strong possibility of trauma having occurred.

The fourth patient was an alcoholic who had abdominal pain for two weeks prior to admission. The serum amylase on admission was elevated and the diagnosis of alcoholic pancreatitis was made. Because of a continually falling hemoglobin, hemorrhagic pancreatitis was diagnosed and the patient was explored. The diagnosis was confirmed; but a ruptured spleen was also found and established as the cause of the falling hemoglobin. Again there was no retrospective history of trauma; but this patient probably was another alcoholic injured while in a stupor and unable to recall the incident.

The final patient presented with a 16-hour history of left anterior chest pain radiating to the left shoulder and arm. He was diaphoretic and nauseated. The pain increased with inspiration and motion of the right shoulder and decreased with sitting. He gave a history of similar pain one month prior to admission which was mild and lasted only minutes. He had a two-to-three-week history of chills and sweats. His blood pressure was 170/110, pulse 80. An electrocardiogram showed a strain pattern. A lung scan indicated a possible pulmonary embolus. The initial abdominal examination was negative. A diagnosis of myocardial infarction or pulmonary embolus was entertained and the patient was started on heparin. Several hours later the blood pressure fell to 90/50 and the abdomen became tender with rebound tenderness and decreased bowel sounds. Exploration revealed a ruptured spleen.

Although there is no definite history of trauma in any of these patients, the first four probably represent simple delayed rupture secondary to trauma. The last patient seemingly fits the classification of occult rupture of the spleen. This would make our series of 114 splenic ruptures include 96 (84.2%) acute traumatic ruptures, 17 (14.9%) delayed traumatic ruptures, and one (0.9%) occult rupture. These figures are virtually identical with the figures quoted by Drapanas[4] for the incidence of acute delayed and occult splenic rupture. His series included 85 percent acute ruptures, 14 percent delayed ruptures, and one percent occult rupture.

These five patients are naturally quite similar to the patients in the isolated injury group with respect to the postoperative stay in the hospital and postoperative morbidity since they do indeed represent simply delayed splenic rupture.

Discussion

The incidence of traumatic rupture of the spleen has increased during the past 11 years, due, it is felt, to the ever increasing automotive congestion on our streets and highways. Another equally important cause of this increase is the general rise in crimes of a violent nature in this metropolitan area. It is interesting to note that in the oldest groups, being a pedestrain was the greatest hazard, suggesting a decreased reaction time as a factor in failing to avoid traumatic injury.

Diagnosis

The diagnosis of rupture of the spleen depended almost wholly upon the history of an injury and the physical examination of the patient, with the most important clues being: (1) evidence of shock, (2) pain, tenderness, or rebound in the left upper quadrant, (3) absent or decreased bowel sounds, and (4) evidence of moderate to severe injury to the area of the left upper quadrant. Any of these, when associated with an increased index of suspicion of the possibility of a ruptured spleen, usually resulted in a peritoneal tap and/or abdominal exploration. The use of radiographic and laboratory findings have been of little value in the diagnosis of an acute rupture of the spleen.

Delayed Rupture

Delayed rupture of the spleen was defined by McIndoe in 1932 as a rupture which became clinically evident to the examining physician more than 48 hours after an injury.[7] It is in this group that x-ray findings, isotope studies, and laboratory findings as well as peritoneal taps assume their greatest value in directing the physician to the correct diagnosis. The presence of a left upper quadrant mass on flat plate of the abdomen, fractured left lower ribs, isotope scans showing splenic defect, and a falling hemoglobin are some of the more frequent useful studies. In some series delayed rupture has been reported from 7 to 41 percent.[1,3,6,9,10,13] Zabinski and Hardy reported a patient with delayed hemorrhage of the spleen occurring two years after the initial trauma.[10] In the presence of other serious injuries, signs of shock, falling hemoglobin, and loss of bowel function may be attributed to other more obvious problems initially, e.g., a fractured pelvis, femur, or vertebral transverse process; and it is in these cases that peritoneal lavage tap has its greatest value.

On multiple occasions the positive tap has been the deciding factor resulting in abdominal exploration, especially when the patient has been unconscious or inebriated. Other reports frequently refer to the latent period of Baudet with additional minor trauma or severe exertion, as with coughing or sneezing, causing further rupture of the spleen with the resultant rapid appearance of symptoms.[8] This, however, did not appear to be the case with the patients in this series whose findings were more insidious in development. Mortality in the delayed rupture group has been reported as high as 10 percent.[9] In this series one of 17 patients was lost (6%), and this was a result of other injuries.

Thrombocytosis

Thrombocytosis after splenectomy in itself is not a significant problem except as related to an increased tendency to thrombosis and thromboembolism. An elevation of the platelet count to 800,000 should be no cause for alarm according to Ballinger,[1] while a "count over one million should suggest the need for temporary anticoagulation with heparin." While three patients in our series developed thrombophlebitis, only one had a significant elevation of the platelet count and that only to 630,000 per mm/3. One patient was anticoagulated at 540,000 without symptoms, while one of 10 patients with counts between 800,000 and one million was anticoagulated, as was also one of five with counts greater than one million.

Splenosis

Splenosis is the peritoneal autotransplantation of splenic tissue following trauma to the spleen and is an infrequent complication of splenic rupture. This was first described by Kuttener in 1910.[2] Splenic implantation usually occurs in the peritoneal cavity but has been reported in other areas of the body, including subcutaneous tissue and thoracic cavity.[2] This may be a silent entity when it occurs in the abdominal cavity or may give rise to vague abdominal discomfort due to growth of the implant. Postoperative adhesions with multiple splenic implants may rarely lead to intestinal obstruction. The time interval between rupture of the spleen and the diagnosis of splenosis has ranged from five months to 30 years. We have been unable to document any case of splenosis in this series.[2]

Pancreatitis

Pancreatitis may develop as a result of pancreatic injury during splenectomy, especially if there is massive hemorrhage from the splenic hylum and the pancreas is closely adherent to the pelvis of the spleen. The pancreatitis which results is usually localized but may progress to a fulminating and fatal process.[1] One patient with an isolated splenic injury developed a pancreatic fistula without pancreatitis. There were three patients with pancreatitis and four with pancreatic fistulae in the multiple injury group. Six of these seven patients with multiple injuries had pancreatic injury noted at but not due to surgery.

Mortality

The mortality of isolated splenic rupture is very low if the condition is recognized early and treated vigorously and should approach

that of anesthesia alone. The mortality of patients with other injuries is due largely to those other injuries. Ballinger[1] states that 25 percent of patients with splenic injuries die; but this figure is misleading since most of those deaths are due to other injuries suffered at the time of the trauma. It was impossible to determine the number of patients with splenic rupture who died before they could be seen in the emergency room and admitted to the surgery service in this hospital. Ballinger reports 10 percent mortality among patients who come to surgery and a 1 percent mortality for patients with isolated splenic rupture.[1] Our mortality was 17.2 percent for the multiple-injury group and 0 for patients with isolated injury.

Spontaneous Rupture

Orloff and Peskin[7] established certain criteria that must be satisfied before the diagnosis of spontaneous rupture of the normal spleen can be made. These include the absence of trauma, perisplenic adhesion, or disease that might adversely affect the spleen, and the lack of any pre-existing anatomic abnormality within the substance of the spleen. It is felt that spontaneous rupture of the normal spleen is an extremely rare, if not nonexistent entity.

Drapanas[4] and Foley[5] describe occult rupture of the spleen as an insidious entity manifested by many, often vague, symptoms which may be misleading and contribute to an erroneous diagnosis. Such diagnoses as angina, myocardial infarction, pulmonary embolism with pleural effusion, intraperitoneal malignancy with palpable mass, a retroperitoneal sarcoma, or a blood dyscrasia have been entertained.[4] Occult rupture usually implies traumatic rupture in a situation where the trauma was insignificant or entirely overlooked, thus leading to the impression that this is a spontaneous process.

Conclusions

(1) Splenic injury is common following abdominal trauma.

(2) Injury to the spleen must always be suspected if the patient shows signs of shock or abdominal injury, especially if there are fractured ribs on the left or other signs of injury to the left side of the trunk.

(3) Splenic injury may be insidious or delayed in its manifestations and, in lieu of exploration, expectant observation should be carried out for at least seven days in any case of moderate to severe trauma to the left side of the trunk.

(4) As an isolated injury, a traumatically ruptured spleen does not result in a great blood requirement or in great morbidity or mortality. These sequelae are usually the result of other associated injuries sustained at the time of the accident.

(5) Pedestrian injuries carry a higher morbidity, mortality, blood requirement and longer hospital stay than other types of injury.

(6) Anticoagulation is not indicated except for specific complications following splenectomy for traumatic rupture.

(7) The entity of spontaneous rupture of the normal spleen is nonexistent and probably represents overlooked trauma.

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Early to bed and early to rise, if you want your head to feel its normal size.

Management of Open Fractures*

An Analysis of 673 Cases

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THE STATEMENT BY HIPPOCRATES that "War is the only proper school for the surgeon" applies well to the surgeon's advances in the management of open fractures. "Adequate debridement" for open fractures was first adopted by Pierre Joseph Desault‡ and popularized by his student Dominique Jean Larrey# who is considered one of the greatest surgeons of all time. In spite of our accumulated knowledge in the treatment of open fractures during the wars, the infection rate still ranges from 10-25%.[1,2,3,6,7,9,10,15]

The primary objective in the management of an open fracture is union with the prevention of wound sepsis. Inadequate surgical care at the time of the initial debridement will result in a potential culture medium for bacterial growth.

Good surgical debridement is probably the most important factor in the management of open fractures and has been emphasized in our teaching for the past 25 years. The difficult technical problem is to determine the adequate debridement of devitalized and contaminated tissue. Scully et al.[11] observed that identification of muscle viability correlated well with the histologic conformation. Muscle color did not appear to be a reliable criterion, but the ability to bleed, consistency and contractility correlated closely with the histologic evaluation.

Materials and Methods

Six hundred two patients with 673 open fractures from Hennepin County General Hospital comprise this series. Fractures of the phalanges, skull, scapula, spine, sternum and pelvis were excluded; the study included fracture dislocations and traumatic amputations (Table 1). Fifty percent of the patients had associated injuries involving intra-abdominal organs, major blood vessels, pelvis, chest and skull. Approximately 65% of the injuries were the result of car or motorcycle accidents or pedestrian injuries. Gunshot wounds and industrial accidents formed only a small percent of the total. From 1961 to 1968, 450 patients with open fractures were examined and their results were compared to 142 open fracture patients seen from 1955 to 1960.

TABLE I
Analysis of Open Fractures
A Fourteen-Year Study (1955-1968)
Hennepin County General Hospital

	Number	%
Total Patients	602	
Total Open Fractures	673	
Complete Wound Healing	539	89
Complete Fracture Healing	451	75

The cases were analyzed by chart reviews and by letter follow-up from the patients who were transferred to private care. Eighty-nine percent of the open fractures were followed for at least a month or until soft tissue healing was present. The time from the moment of injury to the operating room averaged five hours during the period from 1955 to 1960 and three hours during the period from 1961 to 1968. The longest wait for the patient to be brought to the operating room was 12 hours. The average age was 45 years, and the majority of the patients were male.

All patients were directly supervised by the general surgical or orthopedic resident assigned to the trauma service, and in almost every case

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‡1744-1795

#1766-1842

direct or indirect consultation was obtained from a member of the attending staff. The method of treatment has been relatively standard over the past 14 years, although some individual discretion was allowed in the choice, route, dosages of antibiotic and the amount of irrigating solution.

Management

The patient is admitted directly to the treatment room of a surgical ward without preliminary evaluation in the outpatient receiving room. He is briefly examined for overt hemorrhage and other gross systemic injuries. If there is airway obstruction tracheostomy should be done immediately. The open fracture is then adequately splinted and blood is drawn for laboratory studies including blood typing and crossmatching. At least one liter of Ringer's lactate solution is started intravenously as soon as possible, and a subclavian intracatheter may then be inserted to more effectively control the venous pressure, blood pressure and pulse in the multiply injured patient. If shock is present, Ringer's solution is given rapidly until whole blood is available for administration.

The history is obtained if possible and further therapeutic measures such as thoracotomy, gastric suction and insertion of urinary and chest catheters, or both, are done as indicated.

Prophylactic Procedures

When the clinical evaluation is completed, roentgenograms are obtained in the examination room and the operating room is notified of the emergency case. The patient is routinely given 0.5 ml tetanus toxoid subcutaneously and started on intravenous antibiotics. From 1955 to 1960, the combination of drugs used was penicillin and streptomycin, penicillin and terramycin, and penicillin and tetracycline which was changed to penicillin and chloromycetin from 1961-1966. The dual antibiotics were given in much smaller doses and usually only in the postoperative period from 1955-1960. During the last three years the antibiotics used were penicillin or methicillin or oxycillin in large doses in combination with ampicillin or kanamycin. Presently, antibiotics are used for only five days.

The routine use of antibiotics[14,8,12] in elective orthopedic procedures showed a greater rate of infection in cases treated prophylactically; in those studies, however, the antibiotics were started postoperatively and administered in much smaller doses than we prescribed at Hennepin County General Hospital. More recent study[5] revealed an incidence of infection of 1.7% in a treated group and 8.9% in a control group. These patients were given procaine penicillin the night before surgery, the morning of surgery, during surgery and for five days after surgery.

If the wound from an open fracture is potentially contaminated, we give intravenous antibiotics in larger doses before surgery to "sterilize" the healthy tissues adjacent to the devitalized areas. The likelihood of secondary infection by seeding of bacteria to surrounding healthy tissue is diminished with preoperative antibiotic levels that help render the field as sterile as possible.

Definitive Treatment

When the patient's condition stabilizes, he is brought to the operating room. A regional type of anesthesia is preferred, using axillary or supraclavicular blocks for the upper extremities and spinal anesthesia for lower extremities. A circumferential surgical preparation cleaning with soap and water for ten minutes, coating with alcohol and betadine solution have comprised the routine. The extremity is draped free. The wound is thoroughly irrigated (average of 14 liters of saline) and debrided of all contaminated and devitalized tissue. Lacerations may be extended in order to visualize the bone ends.

Internal Fixation

The involved extremity is then redraped and the surgeon changes gowns and gloves. The fracture is finally reduced and internal fixation is applied only when indicated to stabilize the fracture. This is absolutely indicated when there is an accompanying blood vessel injury that has been repaired. The wound is closed in layers and, if necessary, skin may be shifted in order to cover the fracture site. Relaxing incisions are rarely used primarily in order to obtain wound coverage; we prefer to do pri-

mary or delayed skin grafting. In gunshot injuries, particularly the high-velocity type, the wound is left open and closed secondarily in three to five days. Neither drains nor irrigation tubes are routinely placed in the wounds.

Immobilization

Cast or traction devices are applied while the patient is still in the operating room. Roentgenograms are obtained to check the reduction position before the patient is returned to the ward.

Results

The skeletal distribution of open fractures is shown in Table 2.

TABLE 2
Skeletal Distribution of Open Fractures

Bone	Percent
Tibia	45.8
Femur	12.5
Radius	11.3
Ulna	11.3
Carpals, Metacarpals	7.3
Malleoli	6.3
Tarsal	4.5
Metatarsal	4.5
Patella	4.4
Humerus	3.1
Hip	2.1
Elbow	2.4
Clavicle	0.4

Infection

Deep infection involves both soft tissues and the fracture site, and treatment usually requires wide-open drainage and removal of internal fixation apparatus.This degree of involvement does not heal in less than two weeks. Superficial infection involves only the soft tissue, heals within two weeks and usually does not prolong the morbidity period to any significant degree.

The infections were usually evident in the first month after surgery; the majority occurred in the first seven days. There was only one case of infection in the series which became apparent eight weeks after the initial treatment. The infection must have been present but dormant during the eight weeks.

Thirty-eight cases developed gross infections (5.65%) (Table 3). At one month post surgery, 6.05% of the patients exhibited evidence of infection. There were 26 deep infections and 12 superficial infections. Thirty-six cases had cultures obtained from specimens of the draining wounds. Because of the predominance of positive cultures of staphylococcus infection and gram-negative bacteria a combination of drugs such as oxycillin or methicillin and ampicillin or kanamycin would be a better combination than penicillin and chloromycetin. Five draining wounds with negative cultures were treated as superficial infections. Sensitivity studies were done on all pathogenic bacteria recovered and antibiotic programs were changed as indicated.

TABLE 3
Incidence of Infection
673 Open Fractures, 1955-1968

	No. of Open Fractures	No. of Fractures Infected	Per Cent
Gross Infection Rate	673	38	5.65
Corrected Rate After One Month Followup	593	38	6.42
Infection Rate 1955-1960	135	14	11.85
Infection Rate 1960-1968	458	22	4.82

Primary Metallic Fixation

The incidence of infection in relation to metallic fixation is indicated in Tables 4 and 5.

There were 194 patients with tibial fractures treated by cast alone or with Steinmann pins above and below the fracture site and 34 patients by metallic fixation (Table 4). The in-

TABLE 4
Infection Rate in Primary Metallic Fixation vs Cast Treatment in Open Tibial Fractures

	Total No. Cases	Deep Infected Cases	Per Cent	Superficial Infection Cases	Per Cent
A. Cast Treatment Alone or With Pins Above and Below Fracture Site	194	10	5.15	4	2.06
B. Primary Metallic Fixation	34	7	20.6	0	0

cidence of deep infection was respectively 5.15% vs. 20.6%, which is statistically significant. Two patients had skin slough and required skin grafting.

There were 44 open femoral shaft fractures treated by the conservative method of proximal tibial skeletal traction (Table 5). One developed superficial infection and one deep infection. Primary metallic fixation was used in 18 patients. Three patients or 16.6% ($p - 0.01$) developed deep infection; one case resulted in disarticulation and two patients continued to have chronic osteomyelitis.

TABLE 5
Infection Rate in Primary Metallic Fixation in Open Femoral Shaft Fractures

	No. Cases	Infected Cases	Per Cent
Conservative Traction	44	2	4.54
Primary Metallic Fixation	18	3	16.6

Open Method Versus Primary Closure

Primary closure in open fractures means debridement and irrigation and immediate closure of the wound, including skin grafting. Delayed primary closure indicates closure of the wound before appearance of healthy granulation tissue, usually four to five days after initial treatment, while debridement and secondary closure means debridement, irrigation, packing wound open and closure of the skin when healthy granulated tissue appears, varying from 10 to 14 days.

Of the 44 open fractures treated by initial debridement and secondary closure, 20.4% became infected. In 495 primary closures, there were only 29 fractures or 5.8% ($p = .001$) subsequent infections (Table 6), which is very significant. Unfortunately, it is difficult to compare this series because of lack of a standard objective basis for primary or secondary closure. We cannot strongly criticize the delay closure program on the basis of an increased incidence of infection, because these cases also represented the most severely contaminated or extensive injuries. When primary closure of a wound becomes a technical challenge, we feel that there may be open fractures that cannot be closed primarily. When in doubt that an adequate debridement and thorough cleansing have been done on a grossly contaminated wound, the safe guide is "do not close." However, from 1961-1966, there were only 11 (3.5%) open fractures not primarily closed, in comparison to 31 (18.0%) open fractures left open from 1955-1960. From 1967-1968, there were two open fractures left open or 1.3%.

Morbidity

There were 33 deaths in 602 patients. Seven died within 24 hours, 13 within three days and 11 within three weeks. The deaths were related to other associated injuries of the skull, cardiopulmonary system and pelvis. Only one death could be remotely related to infection of the open fracture and a subsequent septicemia. The triad of skull, pelvis, and extremity injuries indicated a very bad prognosis. One patient died suddenly in the outpatient department six weeks after removal of the cast, apparently from massive pulmonary emboli.

There were 14 cases of clinically diagnosed fat emboli, and the treatment ranged from intravenous administration of 5% alcohol heparin program to a more recently instituted program administering high doses of decadron. All patients with fat emboli were given continuously high concentrations of oxygen. All diagnosed cases of fat emboli have survived, and no deaths have appeared to be directly or indirectly related to fat embolization. However, in some of the deaths occurring in the early series, this complication may have occurred but was not clinically recognized.

Discussion

When the presence of infection is established, the wound is opened wide, cultures are obtained and sensitivity studies are subsequently completed. Intramedullary fixation may be retained for fracture stability, but plates and screws are usually removed, leaving the frac-

TABLE 6
Incidence of Infection
Primary Closure vs. Open Method

	Total No. Fractures	No. Infected Cases	Per Cent
Primary Closure of Open Fractures	549	29	5.28
Open Method Followed by Secondary Closure	44	9	20.4

tures stabilized only with plaster. In most cases a suction irrigation system is connected at the time that secondary or delayed closure is completed.

One of the 26 deep infections progressed to an overwhelming septicemia, and the patient died. Other complications included four cases of extensive drainage treated by amputation and four cases of chronically draining sinuses. Superficial infections healed within two weeks without residuals.

Our problems of wound infection in the last two years of our study were associated with segmental open fracture and open fractures associated with severe soft tissue injuries requiring primary amputation. Five out of six segmental fractures (five tibias and one femur) treated in the usual manner described with primary closure became infected. Two resulted in a below the knee amputation and one with a chronic draining sinus. The other two patients healed eventually after one year of multiple procedures. The only patient who was treated with open method and secondary skin grafting did not become infected and the fracture healed primarily.

Three patients with comminuted open fractures associated with severe soft tissue injury required primary amputation. The wounds were closed primarily. All wounds broke down requiring debridement and secondary closure. All cultures were negative for bacteria.

The rate of incidence of infection in the series from 1955 to 1960 was 10.99% and 4% from 1960 to 1968 (Table 3). The decreased incidence from 1960-1968 may be attributed to six factors: (1) formation of a routine after the patient's admission, thus decreasing the period from injury to operative treatment to three hours; (2) massive doses of antibiotics before, during and after surgery; (3) copious irrigation of wounds using an average of 14 liters of physiologic saline solution; (4) primary closure when easily possible (when in doubt of obtaining adequate debridement of contaminated tissue, leave the wound open and do a secondary or delayed closure); (5) primary metallic fixation only when absolutely necessary and most important; (6) the training of residents to perform more *thorough debridement* of the contaminated and devitalized tissues. The use of antibiotics and copious irrigation are subject to question. Clinical research regarding the routine use of antibiotics in open fracture is presently being done.

TABLE 7

Comparison of Fracture Healing Between Open and Closed Tibia-Fibula Fractures (Average Number of Weeks to Full Weight Bearing)

	Transverse	Oblique	Comminuted
Open	39.1	24.9	53.6 (2 nonunion & bone graft)
Closed	33.1	27.3	25.0
Without Internal Fixation (Cast)	28.2	25.4	35.4 (2 nonunion)
Internal Fixation	38.2	28.4	50.8

A separate study[13] in 1960 at Hennepin County General Hospital was done on 153 consecutive tibial fractures to compare the rates of fracture healing between the closed and open tibial fractures and is illustrated in Table 7. Our experience showed that four out of five cases with segmental tibial fractures resulted in a delayed union or nonunion at the lower fracture site that required subsequent bone grafting.

Summary

The methods of treatment and results were analyzed and 89% of the open fractures were followed to soft tissue healing and 75% to complete fracture healing. The incidence of infection in the last eight years was 4%.

The management of open fractures still presents a difficult problem and no rigid standard treatment can be applied to any individual case. In general, however, we recommend these principles of treatment:

(1) Transfer the patient to the operating room as soon as possible. (2) Adequate debridement and copious irrigation. (3) Massive doses of antibiotics, before, during and after surgery. (4) Primary closure whenever possible except in these three major categories. (a) Any segmental fractures of long bones, especially femur, and tibia. (b) Severe open fractures requiring primary amputation. (c) In extensive soft tissue injury or loss of skin, associated with comminuted or segmental open fractures. (5) Avoid primary metallic fixation, particularly intramedullary nailing and plating. (6) A multiply-injured patient represents a multi-specialty problem.

References may be secured from the author or the reprints.

Historic Hospitals

An Early Municipal Hospital, Bruges



St. John's Hospital, Bruges. (Courtesy Official Belgian Tourist Bureau.)

The development of western commerce and industry which began about the eleventh century resulted in the creation or rebirth of almost all of the towns and cities of present-day Europe. For the first time in centuries there existed a class of free city-dwellers who were not responsible to the feudal lords and who were able to provide their own charitable institutions and centers of learning.

The city of Bruges in Flanders was an early industrial center, specializing in the importation of raw wool from the British Isles and its conversion into finished woolen cloth for sale throughout Europe. By the thirteenth century Bruges reached a population of 80,000, about twice that of London.

The free citizens of Bruges early recognized the need for a city hospital; they built the Hospital of St. John in the center of the city. The date of its foundation is undetermined, but it is known to have been admitting patients as early as 1188. Built of brick with high ceilings and tile floors, it provided excellent light and ventilation. Its enclosed garden and view of the canal afforded one of the pleasantest settings in the city.

From its foundation to the present century, St. John's has been staffed by Augustinian brothers and sisters. In addition there was a public medical service as early as 1294. This was a purely civic enterprise that provided two physicians, two surgeons, and eight midwives, all appointed by civic authorities, to minister to the needs of the community.

As in modern cities, the municipal hospital and medical service were kept busy by emergency work and trauma. A fifteenth century chronicle mentions injuries by fire, brawls, collapsing buildings, and children falling into canals, being gored by cattle, struck by windmill sails, and run over by carts. Contagious diseases were treated elsewhere at a plague hospital, probably outside the city walls.

The chief fame of St. John's Hospital today lies in the fact that it is the repository of many of the finest paintings of the Flemish master, Hans Memling.

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Ann Med Hist N.S. IV, 398, 1932. Boissonnade, Life and Work in Medieval Europe, 1927, reprinted by Harper and Row, 1964.

Sanitation

An Enemy of the People

Dr. Stockman: The miraculous springs that cost such a fortune to build, the whole Health Institute, is a pesthole! . . . You know the filth up in Windmill Valley? That stuff that has such a stinking smell? It comes down from the tannery up there, and the same damn poisonous mess comes right out into the blessed, miraculous water we're supposed to *cure* people with!

Hovstad: How are you so sure about this, Doctor?

Dr. Stockman: I had a suspicion about it a long time ago—last year there were too many sick cases among the visitors, typhoid and gastric disturbances. . . . The whole water system has got to be changed. The intake is too low, it's got to be raised to a much higher spot. The whole construction's got to be ripped out! . . . Of course I warned them. When they started the damned thing I told them not to build it down there! But who am I, a mere scientist, to tell politicians where to build a health institute!

Aslaksen: The water system is very important to us little businessmen, Doctor. Kirsten Springs are becoming a gold mine for this town, especially for the property owners, and that is why, in my capacity as chairman of the Property Owners Association . . . I come into contact with all kinds of people, and since I am known to be a law-abiding and solid citizen, I have a certain influence in this town—you might even call it a little power. The citizens of the town are complimenting you for bringing this important matter to everybody's attention. . . . I don't want any wild-eyed radicalism on this thing. I've had enough of that in my time, and no good ever comes of it.

Peter Stockman: I took a little walk over to the city engineer this morning and in the course of conversation I sort of jokingly mentioned these changes—as something we might consider for the future, you know.

Dr. Stockman: The future won't be soon enough, Peter.

Peter Stockman: I don't suppose you have taken the trouble to consider what your proposed changes would cost?

Dr. Stockman: No, I never thought of that.

Peter Stockman: Naturally. Your little project would come to at least three hundred thousand crowns. . . . Oh, don't look so upset—it's only money. The worst thing is that it would take some two years. . . . And what do you propose we do about the springs in the meantime? Shut them up, no doubt! Because we would have to, you know. As soon as the rumor gets around that the water is dangerous, we won't have a visitor left. So that's the picture, Thomas. You have it in your power literally to ruin your own town. . . . Now look, I'm going to lay this out once and for all. You're always barking about authority. If a man gives you an order he's persecuting you. Nothing is important enough to respect once you decide to revolt against your superiors. All right then, I give up. I told you the stakes you are playing for here, and now I am going to give you an order.

Dr. Stockman: What kind of an order?

Peter Stockman: You are going to deny these rumors officially. . . . You simply say that you went into the examination of the water more thoroughly and you find that you overestimated the danger.

Dr. Stockman: My convictions come from the condition of the water. My convictions will change when the water changes, and for no other reason.

Peter Stockman: What are you talking about convictions? You're an official, you keep your convictions to yourself!

Dr. Stockman: To myself? . . . Now you listen to me. I am a doctor and a scientist—

Peter Stockman: This has nothing to do with science!

Dr. Stockman: Peter, I have the right to express my opinions on anything in the world!

Peter Stockman: Not about the Institute—that I forbid. . . . I forbid you as your superior, and when I give orders you obey. . . . Now this is our crisis. We know what this town was without our Institute. We could barely afford to keep the streets in condition. It was a dead, third-rate hamlet. Today we're on the verge of becoming internationally known as a resort. And in time this town will be crowded with fine carriages; great homes will be built here; first-class stores will open all along Main Street. I predict that if we are not defamed and maliciously attacked we will someday be one of the richest and most beautiful resort towns in the world. . . . Has any one of us the right, the "democratic right," as they like to call it, to pick at minor flaws in the springs, to exaggerate the most picayune faults? . . . We live or die on what the outside world thinks of us. I believe there is a line that must be drawn, and if a man decides to cross that line, we the people must finally take him by the collar and declare, "You cannot say that!"

Dr. Stockman: Answer me this! A platoon of soldiers is walking down a road toward the enemy. Every one of them is convinced he is on the right road, the safe road. But two miles ahead stands one lonely man, the outpost. He sees that the road is dangerous, that his comrades are walking into a trap. He runs back, he finds the platoon. Isn't it clear that this man must have the right to warn the majority, to argue with the majority, to fight with the majority if he believes he has the truth? Before many can know something, *one* must know it! . . . It's always the same. Rights are sacred until it hurts for somebody to use them. I beg you now—I realize the cost is great, the inconvenience is great, the risk is great that other towns will get the jump on us while we're rebuilding—

Aslaksen: Doctor, you could have everything you want!

Dr. Stockman: Except the truth. I could have everything but that. . . . But the children are poisoned, the people are poisoned! If the only way I can be a friend of the people is to take charge of that corruption, then I am an enemy! The water is poisoned, poisoned, poisoned! That's the beginning of it and that's the end of it! . . . I'm the enemy—and now you're first going to find out what kind of enemy I am! I will sharpen my pen like a dagger—you, all you friends of the people, are going to bleed before I'm done! See to all the barricades—the truth is coming! Ring the bells, sound the alarm! The truth, the truth is out!*

*From Henrik Ibsen's An Enemy of the People.

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*Thomas Nash (1567-1601), English author, as quoted in A Mirror up to Medicine by A. C. Corcoran, M.D., 1961.



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Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in submate animal species in multiples of the human dose increases the frequency some animal carcinomas. These data cannot be transposed directly to man. possible carcinogenicity due to the estrogens can be neither affirmed nor uted at this time. Close clinical surveillance of all women taking oral conceptives must be continued.

Indication – Demulen is indicated for oral contraception.

Contraindications – Patients with thrombophlebitis, thromboembolic disors, cerebral apoplexy or a past history of these conditions, markedly impred liver function, known or suspected carcinoma of the breast, known or spected estrogen-dependent neoplasia and undiagnosed abnormal genital eding.

Warnings – The physician should be alert to the earliest manifestations of ombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary bolism and retinal thrombosis). Should any of these occur or be suspected drug should be discontinued immediately.

Retrospective studies of morbidity and mortality conducted in Great Britain d studies of morbidity in the United States have shown a statistically sigcant association between thrombophlebitis, pulmonary embolism, and ebral thrombosis and embolism and the use of oral contraceptives. There ve been three principal studies in Britain [1-3] leading to this conclusion, and e[4] in this country. The estimate of the relative risk of thromboembolism in study by Vessey and Doll[3] was about sevenfold, while Sartwell and assotes[4] in the United States found a relative risk of 4.4, meaning that the users several times as likely to undergo thromboembolic disease without evident se as nonusers. The American study also indicated that the risk did not sist after discontinuation of administration, and that it was not enhanced long-continued administration. The American study was not designed to luate a difference between products. However, the study suggested that re might be an increased risk of thromboembolic disease in users of sential products. This risk cannot be quantitated, and further studies to con this finding are desirable.

Discontinue medication pending examination if there is sudden partial or mplete loss of vision, or if there is a sudden onset of proptosis, diplopia or graine. If examination reveals papilledema or retinal vascular lesions medion should be withdrawn.

Since the safety of Demulen in pregnancy has not been demonstrated, it is ommended that for any patient who has missed two consecutive periods gnancy should be ruled out before continuing the contraceptive regimen. he patient has not adhered to the prescribed schedule the possibility of gnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been ntified in the milk of mothers receiving these drugs. The long-range effect he nursing infant cannot be determined at this time.

Precautions – The pretreatment and periodic physical examinations should lude special reference to the breasts and pelvic organs, including apanicolaou smear, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Demulen. Therefore, if such tests are abnormal in a patient taking Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Demulen may mask the onset of the climacteric. The pathologist should be advised of Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives – A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted; anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X, thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

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Editorials

Infection in Open Fractures*

Doctor Gustilo[1] reviews an extensive experience with compound fractures, principally of the femur and tibia. One finding seems very clear: with primary metallic fixation of compound fractures of the tibia or femur, the rate of infection is high.

That infection is the principal cause of failure in treatment of fractures of the long bones is as true now as it was in the 19th century. It has been stated that, prior to Lister's time, the mortality rate in open fractures of the tibia was approximately 40%. Even now, nonunion in open fractures of the tibia is predominantly associated with osteomyelitis.[2] Also, compound fractures are the largest single cause of chronic osteomyelitis of the adult.[3]

In a retrospective and prospective study, Edwards[2] found that, of 18 patients with fractured tibias with severe osteomyelitis, 12 had deep skin necrosis. The critical question that Gustilo attempts to answer is whether or not primary closure should be done. He suggests that it should be done whenever possible, but he very properly qualifies this by excluding severely traumatized extremities. His qualification is extremely important since other investigators have shown a strong correlation between degree of soft tissue injury and subsequent serious wound infection.[2,4]

Gustilo makes no mention of the percentage of compound fractures associated with farming accidents. Two categories of compound fractures carrying a high risk of gas gangrene are those associated with farming accidents and those associated with gunshot wounds, both common injuries in rural Minnesota. In these types of soft tissue injuries, with or without fracture, primary closure should be avoided.

Gustilo concludes that adequate debridement and copious irrigation with saline are important. One might argue about his suggestion of using an average of 14 liters of saline per compound fracture. On the other hand, if it helps the surgeon to devote adequate time to complete debridement, particularly of nonviable muscle, then it is justified. The object of debridement is to remove nonviable tissue as well as contaminants introduced from the outside.

Massive use of antibiotics is recommended by the author. This is a controversial subject since we have no hard data to tell what is massive or how to choose the antibacterial agent. On the other hand, we do not have available a study that is truly prospective and sufficiently randomized to answer the question concerning routine use of antibacterials with compound wounds. Certainly the majority opinion would favor antibacterials. If such a plan is adopted, however, careful data must be kept on all types of infections besides those associated with primary injury. It was pointed out recently that superinfections are among the hazards of antimicrobial therapy.[5]

Gustilo is to be congratulated on his careful study because it points out the need for:

*See page 185.

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Patrick J. Kelly, M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation.

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Competitive Binding Assays in Thyroid Diagnosis

In the December issue of Minnesota Medicine,* Burke discusses the complexities in interpretation of the results of the various methods in current use for evaluating levels of thyroxine in serum. The problem in the past has been that the methods were indirect, and many factors other than thyroid function affected the results. At the moment, many laboratories have the older and established tests available while introducing the newer and more direct tests. The present situation requires that the clinician, as well as the laboratory man, must know the capriciousness of all the tests available. The situation should improve with time as the newer laboratory methods replace the old.

Competitive protein binding techniques involving immunologic and nonimmunologic systems have provided enormous benefits in clinical practice and research related to the thyroid, as well as to medicine in general. The techniques allow not only exquisite sensitivity but also a specificity heretofore impossible in assessment of thyroid function. Presently, the nonimmunologic systems of competitive protein binding allow direct measurement of total and free thyroxine in serum. These procedures should replace the determination of protein-bound iodine (PBI), thyroxine by column, butanol-extractable iodine (BEI), triiodothyronine-resin uptake, and free thyroxine index —all indirect measures of the fractions of thyroxine in serum.

The immunologic system of competitive protein binding, radioimmunoassay, is finding applications in the practice of thyroidology. Currently, methods exist for the radioimmunoassay of both thyrotropin and triiodothyronine in serum. The determination of triiodothyronine may turn out to have significant clinical importance, but evidence to date is inconclusive. The assay of thyrotropin has already assumed significance in the clinical practice of medicine. The radioimmunoassay has been used for routine diagnostic purposes in our laboratory for about two years and is probably the best single test for myxedema of thyroid origin and also for ruling out pituitary failure as the etiologic event in myxedema. A radioimmunoassay for thyrotropin-releasing factor will undoubtedly be forthcoming in the future.

As Burke points out, it might prove helpful if a way of measuring the cellular content of iodothyronines were available. In addition, improved methods are needed for assessing the impact of the iodothyronines on cells, organs, and the whole man.

William E. Mayberry, M.D.
Rochester, Minnesota

*Burke, M.D.: Serum Thyroxine. Minnesota Med 53:1221, 1970.



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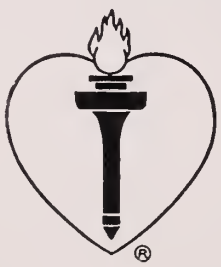
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Hepatic Venous Obstruction

A Glimmer of Hope

THE PAPER by Berthelot, Mignon, and Maillard* presents two examples of acute Budd-Chiari syndrome, presumably secondary to polycythemia vera or Vaquez's disease. For some reason we are given but few angiographic data and no surgical findings. Little is offered to support the major conclusion that emergency treatment is necessary or helpful beyond that which provides support in a terminal situation. During this period, profound changes in hemodynamics associated with destruction of liver cells developed and their patients displayed deep jaundice, ascites, hypocholesterolemia, high transaminases, and renal failure. Fortunately this is a rare condition and is usually easily recognized by the rapid appearance of painful hepatomegaly, ascites, and collateral engorgement, which is variable, depending on the extent of the blockage of the inferior vena cava. Relative contributions of hepatic lymph and lymph from other sources determine the protein content of the ascitic fluid which, as the authors stress, is not consistent.

When the hepatic vein is occluded slowly, the so-called chronic Budd-Chiari syndrome develops. The recent literature has stressed several aspects of this phenomenon, which also is uncommon. It is associated with a spectrum of severity and rapidity of onset which depend on the exact site and nature of the occlusion in relation to the channels available to serve as an outflow tract for the liver. Reports from Japan and England suggest that in many instances the condition previously labeled as "idiopathic" is due to membranous constrictions of one or both hepatic veins and more or less of the adjacent inferior vena cava.[1,2] It is not known how frequently this condition is encountered in the United States.[3,4]

The diagnosis may be difficult since patients with this type of block may appear merely to have ascites associated with cryptogenic cirrhosis. The usual therapeutic measures for ascites may be effective initially. Needle biopsies in such cases are often inadequate and give little hint of severe venous congestion. Later, however, architectural distortion may produce evidence of cirrhosis. One must be prepared to conduct further investigations in young or middle-aged persons with severe ascites who do not present the typical clinical and histologic picture of cirrhosis.

The next step is venography. If a block is demonstrated and is not due to renal cell cancer, hepatoma, or some other neoplasm, there is reason to hope, according to the report of Japanese experience, that surgical relief of the obstruction may be possible by some method such as finger dilation of a web or a shunt fashioned around the obstruction. The technical aspects of these procedures, however, are formidable. The anatomy may be displayed by various x-ray techniques. These are complicated and difficult to interpret. Some appear to be helpful in one situation but not in another. These techniques include inferior vena cava venography from below through a saphenous vein and from above through the right atrium, combined with efforts to inject retrograde into the hepatic veins. Injections of contrast material may be made directly into the liver. Splenic portography and celiac angiography may contribute helpful information. A report from France describes injections between two occlusive balloons in the vena cava to fill various venous channels selectively.[5]

In several cases, thrombosis of hepatic veins in young women using oral contraceptives is reported. It is, of course, difficult to prove a relationship in a given instance, but the reports are impressive. Some patients were too ill to permit adequate investigation and serious consideration of vascular surgery. On the other hand, at least one woman recovered without specific therapy.[4] Additional reports on carefully studied patients with obstruction of the hepatic veins can be anticipated and should provide necessary guidelines to proper therapy.

Douglas B. McGill, M.D.
Rochester, Minnesota

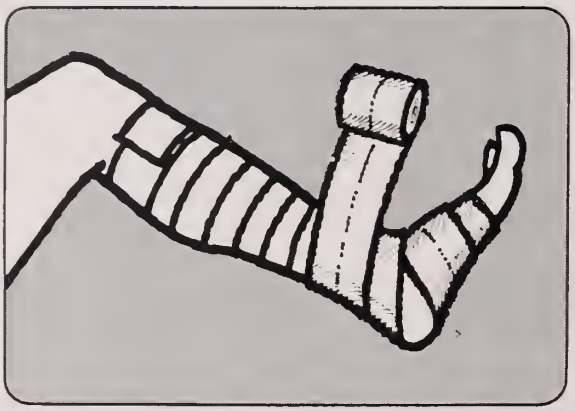
*Berthelot, P., Mignon, F., and Maillard, J-N.: The Acute Budd-Chiari Syndrome: Clinical and Biological Aspects of Two Observations. Minnesota Med 54:97, 1971.

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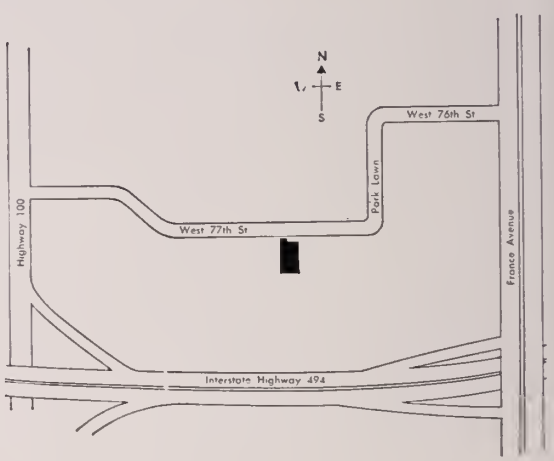
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The Editor's Soliloquy

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Injuries vs Disease

"IT MUST HAVE started that day I slipped on the icy sidewalk in front of the postoffice;" or "It's been bothering me ever since that time I lurched forward when the bus stopped too suddenly." Something must have precipitated it!

To account for elusive aches and pains, twinges and creaks, some folks tend to resurrect some previous event wholly irrelevant to the somatic symptom under discussion. The precise temporal and spatial perimeters of an innocuous past incident provide a neat and convincing cause for the onset of a small ache or a slight pain where there was no ache or pain before.

In the physiologic process of growing progressively and inexorably older, minor disabilities appear as the human organism follows the biologic pattern of dissolution imposed by its species: muscular flabbiness, overweight, joint stiffness, slowed physical and mental responses and reactions, vague malaises due to deliberate excesses or deprivations, the cumulative effect of life's emotional strains and strictures, plus numerous other manifestations all too poignantly familiar to the average mortal.

In mild form most of these signs of aging are inevitable physiologically and have no clinical significance. When exaggerated, however, they indicate a suboptimal physical or emotional state for which the individual may be grossly self-responsible.

To endeavor to establish an exterior etiology which exonerates onself and inculpates a past incident merely delays the relief that might otherwise be obtained.

Is it not possible that the ever-increasing evidence of psychosomatic disease could be iatrogenically aggravated by the physician who is too apathetic to explain the numerous factors that cause physiologic changes in the body from which the symptoms arise? Most physicians are surely aware that preexisting arthritic diseases have their own histologic, pathologic and physiologic course influenced no more than temporarily by minor contusions, strains, or sprains, and that it is fallacious to assign all symptoms thereafter to those insignificant incidents. Though trauma may temporarily aggravate the manifestations of a disease, it very rarely precipitates or significantly alters the course of that disease.

Furthermore, many such physiologic symptoms could be alleviated or even eliminated by the maintenance of prime physical and emotional trim through proper diet, moderate exercise, good hygiene, and a wholesome outlook on life.

But perhaps the cultivaters and cherishers of those common hypochondriases prefer to console and recompense themselves for their symptoms by capitalizing on them to the handsome tune of a lac of rupees.*

Carl O. Rice, M.D.

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INTERNIST NEEDED: To join 9-man, all specialty group of 2 Internists, 2 Surgeons, 2 OB/GYN, 3 Pediatricians. City of 40,000 located 1-hour drive from Milwaukee on Lake Winnebago which serves a medical area of 75,000. Single hospital of 350 beds. Area affords excellent summer and winter recreational facilities. Superior schools, public and parochial and 2 colleges. Excellent initial salary leading to partnership in one year. For further information phone or write: W. G. Kendell, M.D., The Sharpe Clinic, S.C., 92 E. Division Street, Fond du Lac, Wisconsin 54935; Tel. (414) 921-0560.

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(Continued to Page 210)

You May Be Right

Solu-Medrol for Back Pain

We carried out a study on eight male patients suffering from recurrent low back syndrome on the Orthopedic Service of the Veterans Administration Hospital in Montgomery, Alabama. These were all long-term cases which had failed to obtain relief from conventional modes of therapy. We treated these patients by the injection of 125 mg. of Solu-Medrol (methylprednisolone sodium succinate)* intramuscularly every eight hours for three days (nine doses).

The results in all eight cases were most impressive considering the prior intractability and persistence of the conditions. All of the patients reported immediate relief demonstrable by increased mobility and disappearance of pain. Relief lasted for the duration of followup in all but one case. Five cases were followed over nine months, and one patient was followed for eight months after treatment.

The standard treatment modalities for chronic low back syndrome are generally unsatisfactory, and the condition is a frustrating one for the physician and the patient alike. We felt that in this setting a trial with Solu-Medrol was not inappropriate. Large doses of corticosteroids are often given on a short-term basis to patients in shock, so that the safety of the treatment can hardly be questioned. The dosage and duration of treatment were determined arbitrarily; there was no precedent. We wished only to ensure that adequate levels of corticosteroid were available to produce an anti-inflammatory effect. Other dosage regimens might be equally as effective and more convenient: for example, 375 mg. a day for three days.

Since this was a modest trial in only eight patients, it would be presumptuous to predict future therapeutic victories in low back pain. However, we feel that any physician who has patients suffering from low back syndrome might well consider giving Solu-Medrol a trial. Extensions of this treatment are suggested for other conditions of a similar nature. For example, we have made some encouraging preliminary observations in the use of Solu-Medrol for whiplash injuries, intercostal neuralgia, etc. The treatment is relatively inexpensive and can be administered on an outpatient basis.

Harold D. Kletschka, M.D.
L. Clyde Sheehan, M.D.
Montgomery, Alabama

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Some people are all front door. Open that and you are out in the back yard.—Dr. Clyde Wildman, DePauw University

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k, , and Horn, D. B.: Assessment of thyroid function by co ined use of the serum protein-bound iodine and resin uptake of -tr dothyronine, J. Clin. Endocrinol. 25:39 (Jan.) 1965.

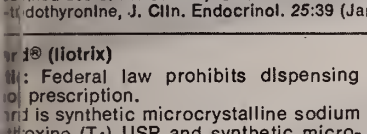
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io: Euthroid provides replacement ther- the thyroactive material normally d by the human thyroid. The normal o gland produces and stores thyro- n, the active components of which are etabolically active hormones: *l*-thy- nd liothyronine. Euthroid (liotrix) pro- s combination of these hormones in , synthetic form, supplied in a con- t 1 ratio in order to simulate as closely sible the physiologic and metabolic c of normal endogenous thyroid secre- s

ntrast with the individual synthetic, a lically active hormones, Euthroid will al produce normal results for PBI, T_3, er thyroid function tests—consistent inical progress—when persons with nous thyroid deficiencies are made y id. Sodium liothyronine (T_3) acts more d and for a shorter period of time than pa tions of biological origin. Custom- s use as a single agent produces in- r iately decreased PBI values. Sodium t oxine (T_4), on the other hand, is more t ound by plasma protein fractions and a ewhat slower acting than sodium y nine (T_3); its use as a single agent d o produce inappropriately elevated ues. Euthroid, with its unvarying 4:1 o T_4/T_3, permits interpretation of ap- p te laboratory tests consistent with the l inical status of the patient.

ic ions: Euthroid (liotrix) provides thyroid la ment therapy in all conditions of in- g te production of thyroid hormones, namely:

1) Hypothyroidism, including cretinism and myxedema.
2) Simple (nontoxic) goiter.
3) Subacute or chronic thyroiditis including Hashimoto's disease.
4) Prevention of goiter in hyperthyroid patients undergoing treatment with thiouracil derivatives.
5) Usage in patients who may manifest intolerance to thyroid products of animal origin.

Contraindications: Acute myocardial infarction, adrenal insufficiency, hypersensitivity to any component of this drug.

Warnings: Liotrix should not be used in the presence of cardiovascular disease unless thyroid replacement therapy is clearly indicated. If the latter exists, low doses should be instituted (Euthroid-1/2 or Euthroid-1) and increased by the same amount in increments at 2-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out and adrenal deficiency due to hypopituitarism corrected before liotrix therapy is started.

If hypothyroidism and adrenal insufficiency exist concomitantly, cortisone or similar steroids should be given at dose levels sufficient to correct the adrenal insufficiency before attempting replacement therapy with thyroid hormones.

Likewise, the possibility of alterations in the prothrombin time must be considered and closely monitored in patients on anticoagulant therapy.

Myxedematous patients are very sensitive to thyroid hormones, and dosage should be started at a very low level and increased gradually.

Precautions: Hypothyroid patients are especially sensitive to thyroid preparations, and those with severe hypothyroidism may be unusually so.

Initiation of thyroid replacement therapy in patients with diabetes must be carefully monitored because of potential fluctuation in daily insulin or oral hypoglycemic requirements.

As with all thyroid preparations, this drug will alter the results of thyroid function tests.

Adverse Reactions: Overdosage or too rapid increase in dosage of thyroid preparations can produce signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration: Initial dosage should be low and gradually increased at 2-week intervals until the desired clinical response is obtained.

Laboratory criteria of euthyroidism include a PBI of 3.5 to 8 mcg; T_3, T_4, and BEI tests are useful.

For most patients, a single daily dose of Euthroid-1, -2, or -3 will maintain euthyroidism. Transfer of a patient from a maintenance dose of another thyroid preparation to Euthroid can usually be effected smoothly. See table for initiating therapy or converting from other thyroid preparations.

Euthroid (liotrix)		Approximate Equivalents Natural Thyroid USP	Synthetic	
Tablet	T_4*/T_3** mcg		T_4*	T_3**
Euthroid-½ pale orange	(30/7.5)	½ grain	.05 mg	12.5 mcg
Euthroid-1 light brown	(60/15)	1 grain	.1 mg	25.0 mcg
Euthroid-2 violet	(120/30)	2 grains	.2 mg	50.0 mcg
Euthroid-3 gray	(180/45)	3 grains	.3 mg	75.0 mcg

*T_4=sodium levothyroxine (*l*-thyroxine)
**T_3=sodium liothyronine (*l*-triiodothyronine)

Dosage for cretinism or severe hypothyroidism in children is the same as for adults with myxedema. Eventual maintenance dosage in the growing child may be higher than in the adult.

Overdosage: *Symptoms*—Headache, instability, nervousness, sweating, tachycardia, and unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm; chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

Treatment—Shock—Supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.

Supplied: Square W/C monogrammed tablets of four potencies, each identified by a different color (see table); bottles of 100 and 1000.

E-GP-11-4C

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(Continued from Page 206)

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LOCUM TENENS—Physician to practice general medicine with multi-specialty group for months of May through August. Popular vacation area with many resorts and recreational opportunities—contact Duane E. Carlson, Business Manager—Bemidji Clinic, Ltd., Bemidji, Minnesota 56601.

ANESTHESIOLOGIST seeks location small city in Minnesota. Age 37, U. S. graduate, Minnesota license. Write Minnesota Medicine—454, 375 Jackson St., St. Paul 55101.

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WANTED: Internists, Obstetrician, Pediatrician, Orthopedist, Generalists, Midland, Texas—Warm, sunny cosmopolitan community, 65,000, highest educational level per capita in country. Easily accessible to ski and mountain resorts. Martha Madsen, M.D., 2200 West Illinois Street, Midland, Texas 79701, 915-683-3206.

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MINNEAPOLIS booming suburb of 10,000 plus surrounding communities is without any physician's services. Desire physicians rent proposed clinic in village near two freeways. Gustafson—612-784-3944.

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University of Sydney, Australian Issue—June, 1971

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Drug Effects—*R. S. Krooth of Ann Arbor, Mich.*
University of Sydney—*John Loewenthal, M.D.*
Inherited Spinal Muscular Atrophies—*C. Kerr, M.D.*
Our Australian Colleagues—*Carl O. Rice, M.D., Editor-in-Chief*
Greetings—*Walter L. Rice, American Ambassador to Australia*
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Manuscripts

Physiological Determinants in Champion Athletes—*A. S. Rebuck, M.B., B.S.*
Allopurinol and Inborn Errors of Purine & Pyrimadine Biosynthesis—
R. M. Fox, M.B. and W. J. O'Sullivan, Ph.D.
Supracondylar Fractures of the Humerus in Children—
E. H. Bates, M.D. and T. K. F. Taylor, M.D
Inborn Errors of Folic Acid Metabolism—*P. B. Rowe, M.B., B.S.*
Treatment of End-Stage Renal Failure by Dialysis—*S. G. R. Sheil, M.S., et al.*
Treatment of Chronic Peptic Ulcer—*D. W. Piper, M.D.*
Amniotic Fluid Analysis in the Determination of Foetel Age—
N. D. Jolls, M.B. and W. R. Jones, Ph.D.
Spinal Muscular Atrophy—*J. G. McLeod, M.B., and I. M. Williams, M.B.*
Development of the Medical School at Univ of Sydney—*Ronald Winton, M.B.*
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The Assessment of Abnormal Illness Behaviour—*I. Pilowsky, M.D.*
The Treatment of Chronic Peptic Ulcer—*D. W. Piper, M.D.*
Diagnosis and Management of Malignant Melanoma—*G. W. Milton, M.D.*
Some Aspects of Occupational Medicine in the Univ. of Sydney—*G. C. Smith, M.D. et al.*
Effect of Lactic Acid Infusion in Dogs—*D. F. J. Halmagyi, M.D. et al.*

The Viewing Box

Left Superior Mediastinal Mass

THE FOLLOWING abnormality was seen on routine preoperative chest roentgenogram prior to a minor surgical procedure in this 44-year-old with no previous medical history other than chronic alcoholism. He denied any chest pain, dyspnea, palpitations, cyanosis, and dysphagia. Blood pressure was essentially within normal limits. Peripheral pulses were regular in rate, rhythm, volume, tension, wave character, and timing in all four extremities.

What Is Your Diagnosis? (See next page)



Figure 1

A diagnosis of pseudocoarctation of aorta was confirmed by the following retrograde femoral aortography and ventriculography with pressure studies.



Figure 2

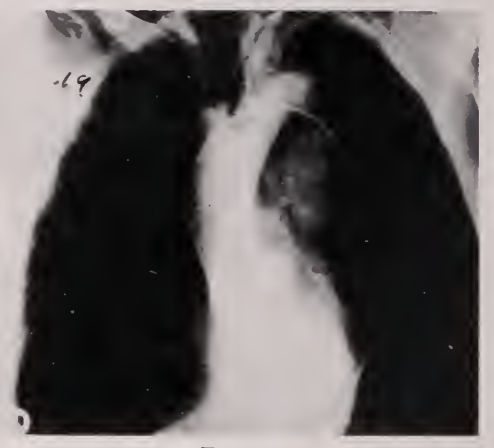


Figure 3

Upon injection of contrast media the ascending aorta was noted to be moderately dilated. A "stenosis" was observed in the thoracic aorta distal to the left subclavian artery. Distal to this point a marked "post-stenotic" dilation of the descending aorta was seen. There was no evidence of any aortic stenosis or insufficiency. The aortic valve was noted to have three cusps. The right and left coronary arteries and their major branches, the sinuses of Valsalva and the left ventricle were normal in appearance. Incidentally observed was a common origin of the left common carotid artery and the innominate arteries.

Pressures, in millimeters of mercury, taken at the time of catheterization are represented as follows:

	SYSTOLIC/DIASTOLIC (MEAN)
Aorta (on entry)	105/70 (80)
Aorta (Valsalva maneuver)	130/90
Left ventricle	110/4.2
Aorta (withdrawal)	110/65 (85)
Proximal and distal to the questionable coarctation	110/70 (85)

Rösler and White[1] in 1931 were the first to describe an unusual elongation and tortuosity of the thoracic aorta in two adults. It was not until 20 years later that Robb,[2] Dotter and Steinberg,[3] and Souders et al.[4] focused more attention on this anomaly. Synonyms include atypical[2] or subclinical[4] coarctation, "kinking"[5] or "buckling"[6] of the aorta. "Pseudocoarctation of the aorta" is the most commonly used term in current literature.

It probably represents an abortive form of true coarctation. Traction of a short and unyielding ligamentum arteriosum as the cause of kinking[5] and other theories of pathogenesis have been reviewed in a recent publication.[12]

Clinically a basal systolic ejection murmur, with radiation to the neck, suprasternal notch and interscapular area is the only auscultatory finding of positive significance. Bruwer and Burchell[5] and Bruwer[7] noted this in nine of the 10 patients they studied. They attributed it to turbulence of blood through the kinked arch of aorta. Steinberg[8] found that four of the 16 cases of pseudocoarctation he reviewed with this classical murmur also had an associated stenosis of the aortic valve. In a more recent series, Nasser and Helmen[9] noted a Grade II-III/VI systolic ejection murmur at the base with radiation to the neck in all eight of their cases. Young et al.[10] note the absence of classical signs of aortic flow obstruction, e.g., hypertension of the upper extremities, diminish-

ed femoral pulses with a pulse lag and increased collateralization of intercostal and internal mammary arteries.

Diagnostic criteria used by Gay and Young[11] included: (1) An abnormal chest roentgenogram (usually left superior mediastinal mass); (2) A differential pressure between arms and legs of less than 25 millimeters of mercury; (3) No evidence of increased collateral circulation; (4) A definitive aortogram.

The first of these abnormalities refers to the double rounded shadow along the left superior mediastinum. The upper mass, although translucent because of its high position in the thorax, may be mistaken for a mediastinal tumor or aneurysm; the lower one may be interpreted as being the aortic nob. Steinberg[8] claims that angiocardiography, however, readily delineates the unusually dilated and deformed arch of the aorta and demonstrates that the lower shadow is actually the dilated ("post-stenotic") descending aorta.



Figure 4

Until recently pseudocoarctation of the aorta was considered by most a "benign" condition, warranting no specific therapy.[10] Following the death of one of the six adult patients reviewed by Gay and Young[11] a more aggressive approach may now be warranted. They felt that death in this case was due to rupture of a dissecting aneurysm probably caused by damage to the arterial wall by turbulence distal to the anomaly. A second patient refused surgery and within four years had a "stroke" resulting in hemiparesis and aphasia. The remaining four underwent surgery (resection in three, division of the ligamentum and aortorrhaphy in the other) and are alive and without symptoms one to eight years postoperatively. Subsequent to this report, however, Dungan et al.[12] published four cases of pseudocoarctation in childhood, two of which underwent exploratory thoracotomy which was felt to be unnecessary.

Indications for surgery for pseudocoarctation are still unclear from the various publications on the anomaly.

The appropriate management of the condition remains to be determined. However, awareness of its existence and the steps which should be followed to distinguish it from true coarctation are important for any physician whose index of suspicion is aroused by the abnormality on a routine roentgenogram as shown initially.

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Family Practice

The Family Practice Residency Training Concept

ROBERT KOSHNICK, M.D.*

FAMILY PRACTICE AS a specialty received its approval in February, 1969, from the Advisory Board for Medical Specialties. Since that time, there have been 46 family practice residency programs approved by the American Board of Family Practice.[1] However, as of this year, there are only 286 doctors in family practice training, with only 124 or about 1.5% of the 1970 medical school graduates in the first year of family practice training.

Why Family Practice?

In 1930, there were about 112,000 general practitioners; however, by 1965, this had dropped to 66,000.[3] In 1930, general practitioners outnumbered specialists 70 to 30, but today the GP specialist ratio is 21 to 79 percent.[4] While about 50% of students entering medical school want to go into general practice, by graduation this has been whittled down to 20%.[5] Many of these get specialty training later.

Until this century, the majority of physicians were trained by apprenticeships. This provided a good model for physicians to be generalists. With the Flexner report, medical training was broken down into basic science years and clinical years. As medicine expanded, the teaching was taken over entirely by specialists. Research funding of medical education led to even greater specialization. Academic machinery to train generalists, until now, had not been set up to balance this trend.

Several other trends have further outdated our present mode of training physicians. The first is that the nature of disease treated has changed radically. In the past, most people died of acute infectious diseases such as influenza, pneumonia, dysentery, tuberculosis, malaria, etc. Now the chief causes of death are heart disease, stroke or other vascular problems, and cancer—all chronic in nature. Diabetes, nephritis, hypertension, and psychosomatic problems are further examples of con-

*Second-year Family Practice Resident of Hennepin County General Hospital.



Fig. 1—Hennepin County Family Practice Clinic

tinuing problems for which there are no immediate cures. Most medical care in the past was given for episodic, unrelated acute illness, but now the problem is to treat patients with recurring episodes of chronic illnesses. Crisis-orientated, hospital-based medicine is less applicable than it was in the past.[6]

A second trend has been that towards a health team approach. With the expansion of knowledge, many new paramedical workers have been added: physical therapists, occupational therapists, clinical psychologists, social workers, dietitians, etc. It is estimated that a third to two thirds of the work now done by physicians could be done by paramedical personnel, including nurses and physician assistants who take two to five years to train rather than 10 to 12. We have deemphasized the coordinator of care, the generalist, and replaced him with a rapidly proliferating but uncoordinated mass of specialists.[7] Many recognize that what is needed now is a leader or coordinator of a multi-professional primary health care team.

A third but slower trend has been the gradually increasing sense of potency in the "soft" areas of medicine. Many have stated that 70 or 80 percent of patients have a contributing psychological component to their illness. Familial patterns of stress and illness are frequently ignored when seen because physicians have not been trained to handle them or have not been able to treat them dealing with only one family member. Family pathology, intrafamilial conflict, and sexual and marital problems cannot be dealt with by treating only one member of the family. Physicians have not been trained to look at familial interaction and the role that disruption of familial homeostasis plays in disease.

The Family Practice Program

The family practice element is introduced in the first year of residency (equivalent to the internship) when limited numbers of families are assigned to the trainee as his responsibility. This is increased in the second year and, by the third year, the major portion of the training is in the family practice clinic enrivonment. The family practice residents, supervised by a full-time family practice staff, have total responsibility for the patients in their family groups, not only in the clinics but also taking night calls as problems arise within the families and supervising the in-patient care if their patients need hospitalization. The schematic drawing demonstrates the progressively increasing family practice clinic responsibilities and behavioral science training with decreasing in-patient specialty service training through the three-year residency.

The traditional training in the established specialties is for the family practice resident to spend time learning the skills, techniques, and

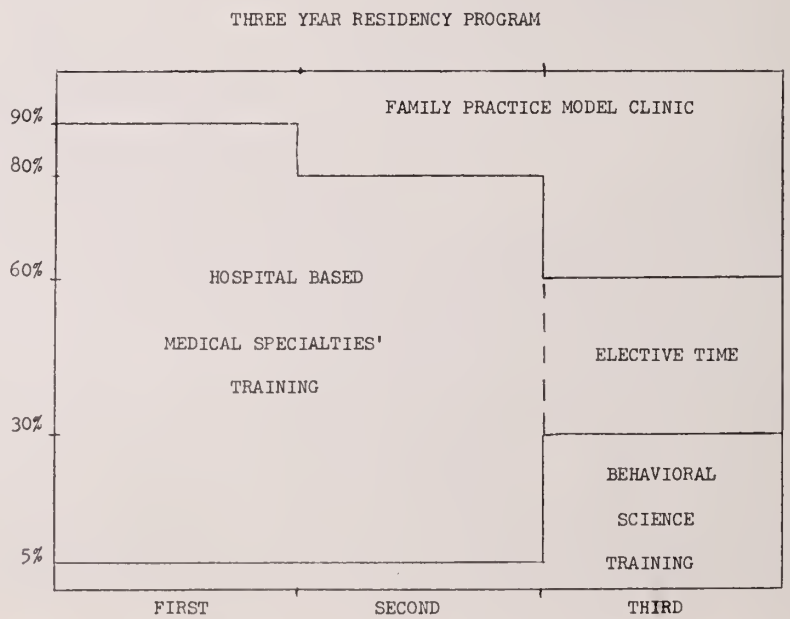


Fig. 2—Diagram of three-year residency program.

procedures of medicine, pediatrics, obstetrics and gynecology, psychiatry, neurology, physical medicine and rehabilitation and, to a more optional and variable extent, surgery and other electives. Experience in certain subspecialties, such as dermatology, ear-nose-throat, ophthalmology, proctology and urology is being gained electively by spending time with interested specialists in their private practices. A distinctly unique element of family practice residencies is the behavioral science training that will be given. Instruction and seminars in marriage counseling, human sexuality, human behavior, medical sociology, community resources, economics of private practice and of health care delivery systems, medical record systems, and other interdisciplinary health seminars (ecology, communications, epidemiology, public health, etc.) are examples of what will be included.

At the end of the third year of residency, the resident will became eligible to take the examination by the Board of Family Practice and will be certified as a specialist in Family Practice. Temporarily for the next decade the certifying board also tests practice-eligible candidates. This requires membership in the AAGP with recertification for membership by the Academy for the immediate past two or more successive three-year periods. Recertification examinations to maintain this specialty status will be required every six years.

Family practice residency programs are effectively bringing family doctors back into teaching, where they can provide medical students and residents with a personal model that they can imitate as well as a specialty with which they can identify. The additional practical experience and theoretical background promises to better equip the doctors who complete this training to perform, function and yet enjoy family practice as a vocational commitment. All of this is greatly increasing student interest and recruitment into this vital area of medicine.

The Trend?

It has been suggested that there have been four periods of major emphasis in medicine. The era of the general practitioner lasted until about 1939. The era of the specialist, doctors trained in the techniques and procedures in a narrowly defined area, spanned 1939 to 1950. The era of the medical scientists who advanced medical knowledge extended from 1950 until the last two years. We are now entering an era of emphasis on community medicine with the top priority of training the generalist skilled in the care of patients. The goal is to produce a new type of highly competent, comprehensive, primary-care physician in sufficient numbers to effectively and efficiently coordinate the medical health team service to the American public.

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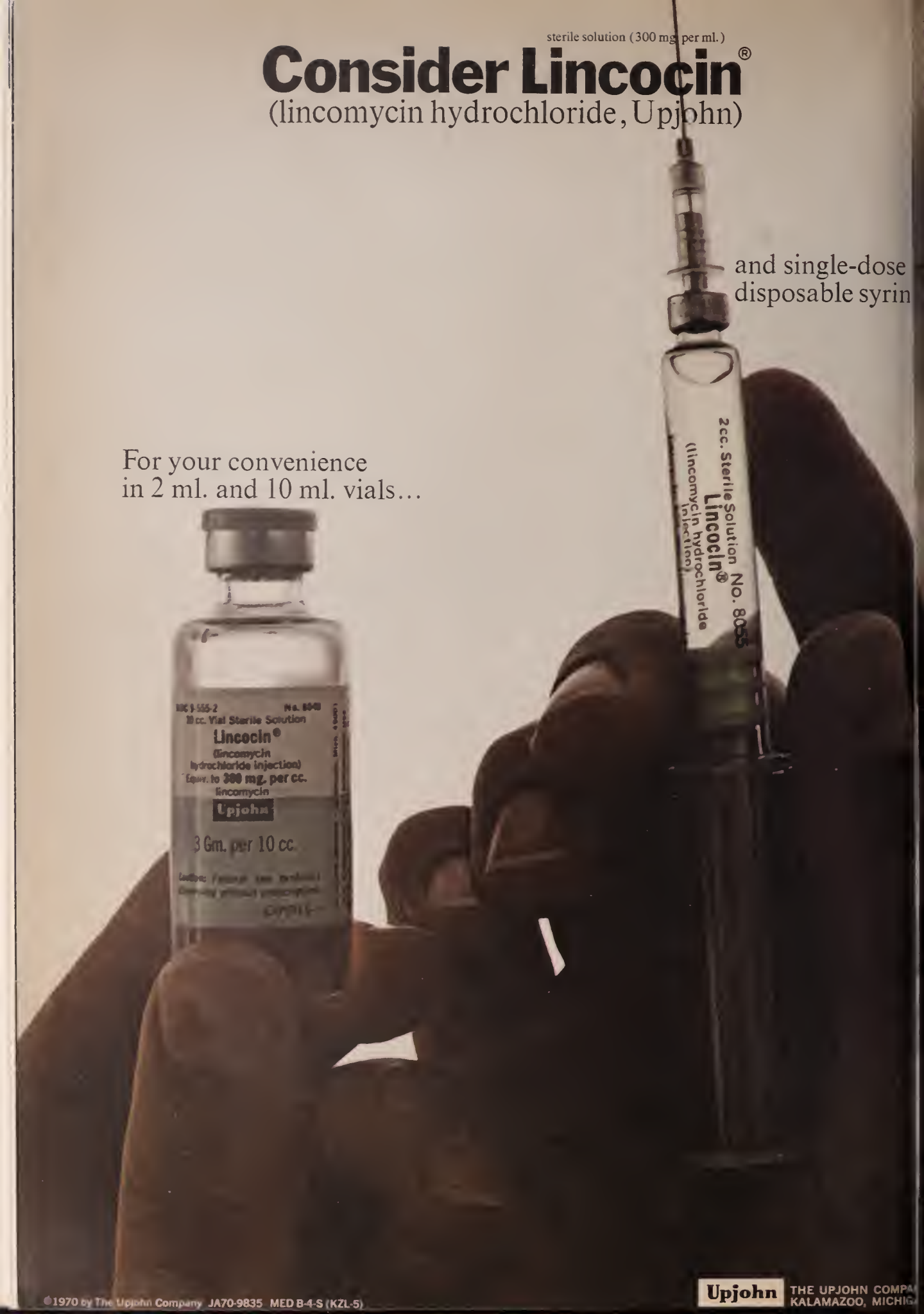
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Obstetrics/Gynecology

Management of Incomplete Abortion with Vacuum Curettage*

DAVID L. HILL, M.D.†

VACUUM CURETTAGE has become a widely accepted method in therapeutic abortion, and many reports have been published concerning it.[2] While this method is equally applicable to the treatment of incomplete abortion, very little experience has been cited in the literature,[1,4,5] as those who have published have not taken full advantage of the method.

Peretz reported a large series and concluded that vacuum curettage was useful only in early abortion (12 weeks or less). Eaton has extended the method to late abortions (13-20 weeks) but, in this group, still recommends a follow-up instrument curettage in the operating room under anesthesia.

Method

The present study was undertaken to document the advantages of vacuum curettage over instrument curettage in the treatment of incomplete abortion. By altering the method of management of late abortion, these patients were also considered as candidates for vacuum curettage as the only operative treatment without anesthesia. Complications were also analyzed to determine if there was any contraindication to using this method as an outpatient procedure. Specific attention was given to septic abortions.

As a comparative control group, all 129 patients admitted to Hennepin County General Hospital in 1968 with the diagnosis of abortion were reviewed. Starting in April of 1969, 100 consecutive patients with the diagnosis of abortion were aspirated even though some were considered clinically complete.

Procedure

The procedure was done in the treatment room immediately following the admission examination on all pregnancies 12 weeks or under. Pregnancies over 12 weeks with no tissue passed were given intravenous oxytocin in a continuous drip until the major products of conception were passed. This was followed immediately with a vacuum curettage. All patients were given intravenous Demerol and Valium; methergine 0.4 milligram was given intramuscularly at the onset of the procedure. All procedures were done by residents who had had no previous experience with the technique. All tissue obtained was submitted for microscopic examination. Blood loss was grossly estimated.

Originally, patients were observed for three days for complications, such as hemorrhage and infection; but at the end of the study they went home on the day following aspiration.

Results

Use of Operating Room

In the vacuum curettage group, only two patients had an instrument curettage performed in the operating room (Table 1), compared with the 55 patients (43%) in the 1968 group.

TABLE 1
Comparison of Total Groups

	129 1968 Group	100 Vacuum Curettage Group
Operating Room Procedure	43%	2%
Anesthesia	45%	2%
Placenta Remaining	77%	60%
Transfusion Rate	23%	17%
Post-Procedure Infections	9%	0%
Perforations	0%	0%

Anesthesia

Anesthesia used for curettage in the 1968 group was general, 27 (37%), spinal, 20 (27%), and local, 11 (15%). Intravenous analgesia was used for the remaining 16 (21%). Although there is no need for dilatation of the cervix in incomplete abortion, instrumentation can be painful and thus require major anesthesia. All patients in the vacuum curettage group received analgesia only, with the exception of the two patients requiring subsequent instrument curettage.

Tissue Obtained From Curettage

Microscopic examination was performed on

*Presented at The Minnesota Obstetrical and Gynecological Society Meeting on April 25, 1970, in Rochester, Minnesota.

†Department of Obstetrics and Gynecology of Hennepin County General Hospital of Minneapolis, Minnesota, and the University of Minnesota Medical School.

tissue obtained from each curettage. In the 1968 group, placental tissue was found in 77% and in 60% of the vacuum curettage group. Essentially the same number of late abortions as early abortions had placental tissue remaining. The ability to predict completeness clinically was poor. Many patients who would have been considered complete had large amounts of placental tissue remaining.

Hemorrhage and Transfusion

Accurate determination of the blood loss in relation to abortion is virtually impossible to obtain. Of the 1968 group 23% required transfusion as compared with 17% of the vacuum curettage group, suggesting that the time factor is important.

Ease and Time of the Procedure

The simplicity of the procedure is best indicated by the fact that after only one demonstration of technique, all resident physicians were able to do the procedure and, after only a limited experience with vacuum curettage, had confidence in its completeness. The operators felt that the technical aspect of the procedure was easy in 94% of the cases. Those 6% that were difficult were directly related to the patient's lack of cooperation.

In terms of the time required for vacuum curettage, it adds an average of five minutes to the initial pelvic examination. The actual time spent aspirating is less than two minutes.

Patient's Acceptance

In the vacuum curettage group, the examining physician estimated the patient's acceptance of the procedure as follows: Good: 67%, Fair: 21%, Poor: 12%. The patient's reaction was directly related to her anxiety level, cooperativeness, and rapport with the operating physician. In no instance was it impossible to complete the curettage.

Vacuum Curettage Patients Requiring Instrument Curettage

In the vacuum curettage group, there were two patients who ultimately were taken to the operating room for instrument curettage for persistent bleeding.

The first patient was from early in the study. A spontaneous abortion at 10 weeks was followed by vacuum curettage. Her bleeding persisted, and she had retained placental tissue at instrument curettage.

The second patient was taking anticoagulant medication for thrombophlebitis with a prothrombin time of twice normal. Vacuum curettage obtained placental tissue, but bleeding persisted. Rather than take the chance of missing retained tissue, an instrument curettage was performed with no placental tissue obtained. Her bleeding stopped when her prothrombin time returned to normal.

Febrile Patients

In the 1968 group, 11 patients (9%) became febrile after an instrument curettage, with no focus of infection detectable other than a tender uterus. These patients were diagnosed as having post-abortive endometritis. There were no patients with this diagnosis in the vacuum curettage group.

Septic Abortions

The number of septic abortions in each group was comparable, 16% in 1968, and 16% in the vacuum curettage group (Table 2). In both groups there were more late abortions than early abortions.

TABLE 2
Comparison of Septic Abortions

	1968 Group	Vacuum Curettage Group
Total Patients	20	16
Operative Procedure (instrument curettage or vacuum curettage)	16	16
Operating Room Procedure	16	0
Anesthesia	16	0
Afebrile Post Procedure	24-36 hours	8-24 hours
Hypothermic Post Procedure	5	0
Severe Complications	1	0

In 1968, it was routine treatment to give antibiotics and oxytocin immediately, but to delay instrument curettage until after 24 hours of the above treatment. Of the 1968 group, 18 of 20 patients had an instrument curettage, 16 of these in the operating room under anesthesia. These patients became afebrile, on the average, between 24 to 36 hours after curettage. Five patients who had an instrument

curettage were hypothermic (T — 95° - 97°) in the first 24 hours after curettage. The average time in the hospital was five days.

In the vacuum curettage group, no patients were taken to the operating room and no anesthesia was given. Antibiotics and oxytocin were started immediately. In the late septic abortions, oxytocin was used to empty the uterus of the fetus and placenta, and vacuum curettage was performed immediately after. This took no longer than 12 hours in any case and usually was accomplished in two to four hours. All patients became afebrile in the range of eight to 24 hours, and none was observed to be hypothermic. The average hospitalization was four days.

Major Complications of Septic Abortions

There were no major complications in the vacuum curettage group.

In the 1968 group, one patient had a severe pelvic infection that required hysterectomy and bilateral salpingo-oophorectomy.

The patient was an 18-year-old who, two days before admission, had a criminally induced abortion at 18 weeks gestation. Cramps, bleeding, fever, and chills brought the patient to the hospital with the fetus still in utero. Temperature on admission was 104°. Antibiotics and oxytocin were started immediately. The fetus and placenta were passed three hours after admission. Bleeding persisted and a gentle instrument curettage was performed in the treatment room without anesthesia five hours after admission. Fourteen hours after admission, a complete instrument curettage, under anesthesia, was done because of persistent bleeding and fever. There was a period of hypothermia postoperatively. Her condition briefly improved, but then deteriorated. On the fourth hospital day she was taken to surgery for a total hysterectomy and bilateral salpingo-oophorectomy necessitated by overwhelming infection. The patient finally left the hospital after 34 days and two more laparotomies which were required for hemorrhage and abscess formation.

Follow-Up

In the vacuum curettage group, 47% of the patients returned to the clinic. One patient had significant bleeding two weeks after vacuum curettage. She was readmitted, and a repeat vacuum curettage yielded no placental tissue. Her bleeding stopped and normal menses were resumed. All other patients seen reported normal menses.

Comments

A major problem of non-septic abortions is the determination of whether there is any tissue remaining in the uterus. At the present time, the choice is to wait and do nothing, or to subject the patient to an operating room procedure and anesthesia. The decision must be made by clinical evaluation.

In this series of 229 patients, it was found that two out of three patients admitted had placental tissue remaining in the uterus. There is no difference in this ratio in early and late abortion. Clinical impression was found to be unreliable in predicting which patients had placental tissue remaining in the uterus.

Vacuum curettage presents an answer to this problem. Here is a method that is easily mastered by any physician. It adds only five minutes to the admission pelvic examination. The procedure is well accepted by the patient and saves an operating-room procedure and the risk of anesthesia. The speed of the procedure reduces blood loss and, in some cases, can prevent the need for transfusion. There are fewer postoperative infections, probably due to less trauma with vacuum aspiration.[3] Even in late abortions, as treated here, there is no need for instrument curettage or anesthesia as recommended by Eaton. Our patients were not checked after vacuum aspiration with instrument curettage. Only one patient had retained tissue after vacuum curettage and required further treatment for this. While our follow-up is not complete, we are the only alternative for care for most of the patients treated, and so we have concluded indirectly that no significant complications occurred since our patients have no other alternative for medical care.

In regard to non-septic abortion, vacuum curettage is the answer to the question of retained tissue in all abortions, early and late. This procedure should be done on every patient, allowing her to return to normal activity at the earliest possible time, assured that the miscarriage is complete. Complications not apparent at the time of examination occurred in only two patients in this series, and these were both evident in the immediate postoperative period. This gives adequate support to the proposal of sending patients home after an uncomplicated vacuum curettage and eliminating hospitalization.

Septic abortions fall into a separate category.

Their serious complications make aggressive management advisable. Vacuum curettage is without doubt the treatment of choice when sepsis is a consideration. Advantages are the speed of removal of infected tissue, the lack of need for anesthesia, and a more gentle handling of tissue to keep spread of infection at a minimum. In this series, the vacuum curettage group had temperatures return to normal sooner than the 1968 group, which had five cases of post-curettage hypothermia, implying a bacterial seeding of the blood stream. There were no cases of hypothermia in the vacuum curettage group.

Conclusions

While there will always be serious complications of septic abortion, the method of treatment can certainly prevent many of these problems. We believe that if handled by immediate vacuum curettage, the serious complications may never occur. Vacuum curettage offers the fastest, safest, most complete, least traumatic method of emptying the uterus of septic contents.

Summary

Vacuum curettage as management of 100 incomplete abortions was compared with a control group of 129 patients admitted for incomplete abortions.

The vacuum curettage group demonstrated the advantages of less blood loss, fewer post-procedure infections, and hospital time saved. Also the need for anesthesia and an operating room were eliminated. The indication for the use of vacuum curettage in septic abortions is primary.

The results of the study suggest that selected patients could be treated in an emergency or treatment room and sent home after a short period of observation.

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Of Death and How it Findeth A Man*

How many means and ways has death to surprise us! Who would ever have imagined that a Duke of Brittany should have become stifled to death in a throng of people? Hast thou not seen one of our late kings slain in the midst of his sports? and one of his ancestors die miserably by the throw of a hog? Aeschylus, forethreatened by the fall of a house, when he was most on his guard was struck dead by the fall of a tortoise-shell from the talons of a flying eagle. Another was choked by a grape-pip. An emperor died from the scratch of a comb; Aemilius Lepidus from hitting his foot against a door sill; Aufidius from stumbling against the door as he was entering the council chamber; Caius Julius, a physician, while anointing a patient's eyes had his own closed by death. And if among these examples I may add one of a brother of mine, Captain St. Martin, playing at tennis, received a blow with a ball a little above the right ear and, without any appearance of bruise or hurt, never sitting or resting, died within six hours afterward of an apoplexy. These so frequent and ordinary examples being ever before our eyes, why should it not continually seem to us that death is ever at hand ready to take us by the throat?

It is uncertain where death looks for us; let us look for her everywhere.

*Montaigne (1533-1592)

This past season, many people went south for the winter. And there it was.—Changing Times.

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Brief Summary

Indications

Erythrocin is indicated against gram-positive cocci — staphylococci (most strains), pneumococci and streptococci (including enterococci). Active against other pathogens, such as *Corynebacterium, Hemophilus, Clostridium, Neisseria,* and *Treponema pallidum,* the agents causing trachoma and lymphogranuloma venereum and primary atypical pneumonia caused by *Mycoplasma pneumoniae* (Eaton agent). Establish susceptibility of pathogenic organism when practical. Maintain therapeutic levels for ten days in the treatment of streptococcal infections to help prevent rheumatic fever and glomerulonephritis. Also consider local measures or surgery whenever indicated.

Contraindications

Known hypersensitivity to erythromycin. I.M. preparation also contraindicated in patients hypersensitive to the "caine" type of local anesthetics.

Precautions, Side Effects

Occasionally abdominal discomfort, cramping, nausea or vomiting may occur; generally controlled by reduction of dosage. Mild allergic reactions, such as urticaria and other skin rashes, may occur. Serious allergic reactions have been extremely infrequent; if hypersensitivity is encountered consider appropriate countermeasures, e. g., epinephrine, steroids, etc., and withdraw drug. The rare possibility of overgrowth of nonsusceptible organisms should be kept in mind; if it occurs withdraw drug and institute appropriate treatment. Local venous discomfort, generally mild, may occur with I. V. administration. I.M. preparation is suitable for deep intramuscular administration only; restrict use in children with small muscle mass. A mild transient local discomfort sometimes occurs following rectal insertion of Erythrocin Suppositories; discontinue if significant discomfort persists.

Administration and Dosage

I. ORAL: In adults with mild to moderate infections caused by readily-susceptible organisms 1.0 Gm. daily; more severe infections or those caused by less susceptible organisms 2.0 Grams daily; unusually severe infections up to 4 or more Gm./day. Daily dose in children is 15 to 25 mg./lb./day depending upon severity of infection. Daily dose should be administered in divided doses at 4-to-6 hour intervals. Continue treatment for at least 48 hours after symptoms have subsided and temperature has returned to normal. In fulminating or life-threatening infections, a parenteral form of erythromycin is preferred.

II. PARENTERAL: Intravenous administration may be continuous or intermittent (6 to 8 hour intervals); 1 to 4 Gm. daily in adults; 15 to 25 mg./lb./day in children, depending upon severity of infection. Recommended I.M. dose is 100 mg. (2 ml.) for adults, 50 mg. (1 ml.) for children 30 lbs. or more and 1.4 to 1.8 mg./lb. in smaller children. Injections are usually given at 6 to 8 hour intervals; may be given at 4 to 6 hour intervals for severe infections.

III. RECTAL: Following therapeutic doses are recommended in children: to 20 lbs., 1-125 mg. suppository every 8 hours; 20 to 40 lbs., 1-125 mg. suppository every 6 hours.

Change to oral therapy as soon as practicable.

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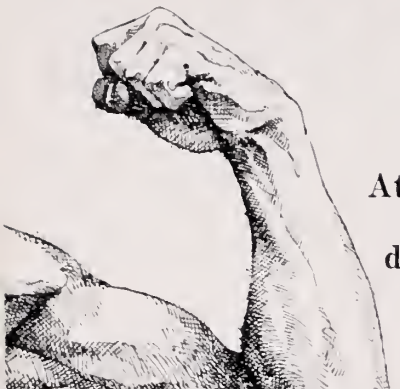
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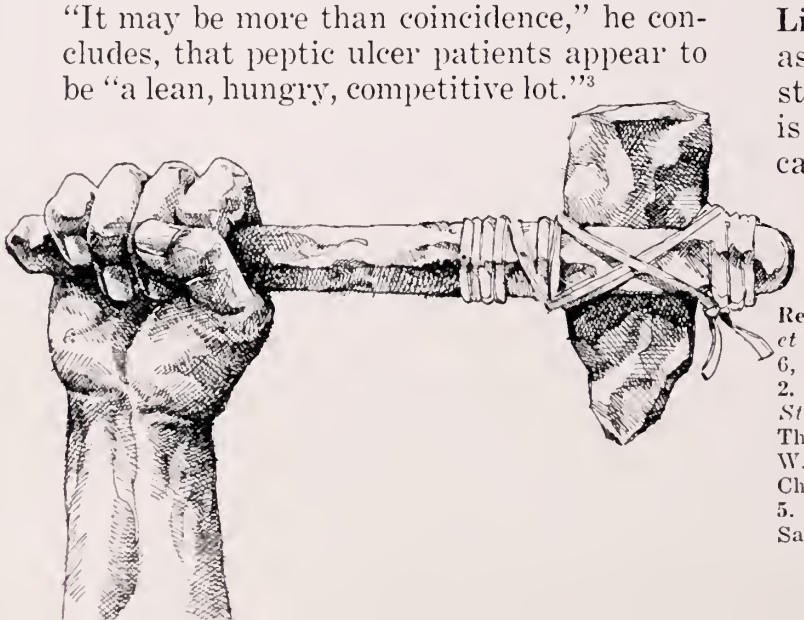
IF MORE MEN CRIE



At least seventy-five out of one hundred adults with duodenal ulcers are men.[1] Why? It may be significant that duodenal ulcer patients tend to crave recognition and are "especially vulnerable to threats to their manly assertive independence."[2]

Hypersecretion—an atavistic response. Stewart Wolf, who, with Harold G. Wolff, studied the personalities of duodenal ulcer patients, wonders if masculine competitiveness is related to "an atavistic urge to devour an adversary." It is striking, he reports, that an accentuation of gastric acid secretion and motility can be "induced in ulcer patients by discussions that arouse feelings of inadequacy, frustration and resentment."[2]

By chance? A lean, hungry lot. Was the link between emotions and gastric hyperacidity acquired through mutation to serve a purpose? During man's jungle period of evolution, the investigator points out, a male dealt with a foe by killing and devouring it. "It may be more than coincidence," he concludes, that peptic ulcer patients appear to be "a lean, hungry, competitive lot."[3]



Big boys don't cry. If more men i maybe fewer would wind up with duo ulcers. But men will be men—the sum to their genes and wha are taught. Schotts observes that w mother admonish son who has hurt hi that big boys don't cr is teachin stoicism.[4] Crying negation of every society thinks of as m A boy starts defendi manhood at an early

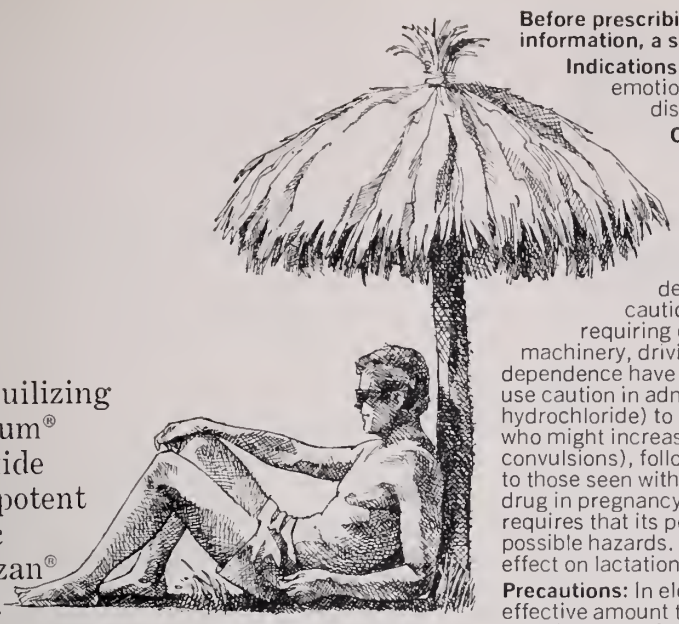


Take away st you can take away sympt

There is no question that stress pl role in the etiology of duodenal u Alvarez[5] observes that many a man wi ulcer loses his symptoms the day he shu the office and starts out on a vacation. problem is, the type of man likely to ha ulcer is the type least likely to take vacations or take it easy at work.

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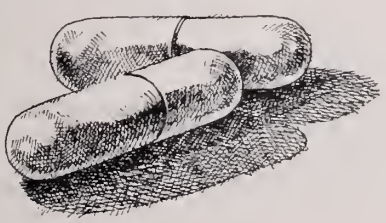
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Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

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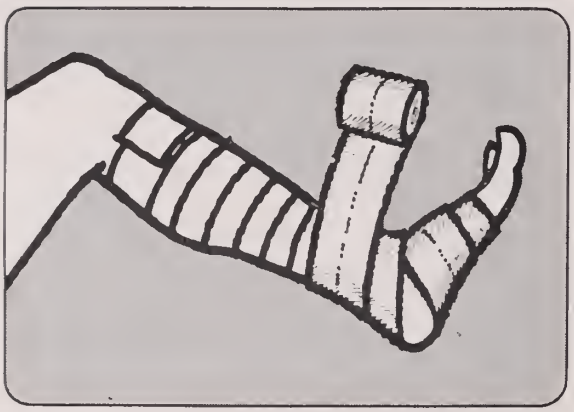
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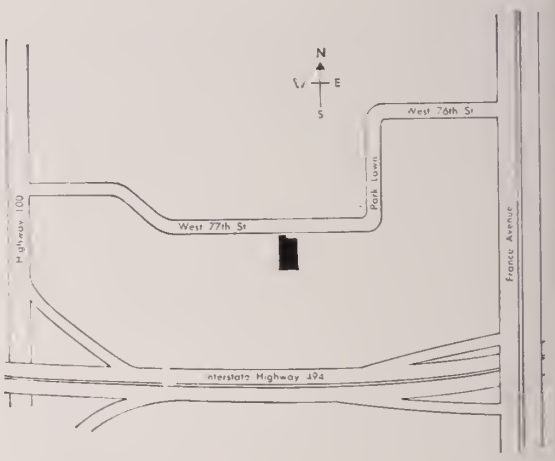
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President's Letter

Catastrophic Illness

Giving authority to the federal government to correct whatever seems to be wrong in society is the current pattern of "social action." It is based on the assumption that the government will and can get the job done effectively. This is not always borne out by the record. Yet the inevitability of increasing participation by the government in health-care fields should be recognized by all of us, regardless of our personal views concerning its desirability. The controlling forces in both our major political parties are committed to a policy of change—not necessarily perfection—in the nation's health-care delivery system.

If we accept this notion that the government will attempt to provide what the consumer public wants, then we should accept the idea that there is a place for government, medicine and the consumer to work together to solve the very real health-care problems which exist today. For instance, it is my very strong opinion that there is a need for a federal health program to meet the needs of unfortunate Americans struck by catastrophic illnesses. These are the illnesses which dissipate life savings and which are economically disastrous for many families. This is a problem which can and should be solved, not by physicians alone, nor by the government or taxpaying consumer alone, but by the three parties working together.

It simply does not make very good fiscal sense to spend billions of dollars to pay the medical bills of many healthy and wealthy Americans simply because they happen to meet the criterion of having lived 65 years, while the disgraceful situation of catastrophic illness continues to bankrupt many families and to derange both local and national economy. If we are the dedicated, compassionate physicians that we like to think we are, we should be leaders in promoting legislation which, if it cannot entirely prevent such demoralizing tragedy, can at least ameliorate it.

Many physicians in Minnesota have had their postgraduate training at Hennepin County General Hospital, to which the March issue and this issue of Minnesota Medicine are dedicated.

R. J. Jackman

Raymond J. Jackman, M.D., President,
Minnesota State Medical Association



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The Capricious Odontoid Fracture

EDWARD L. SELJESKOG, M.D.* and SHELLEY N. CHOU, M.D.*

With the ever expanding problem of automobile accidents occurring on our streets and highways, hospital emergency room facilities are witnessing ever increasing numbers of seriously injured patients. Obviously, these trauma problems are multiple in type, beginning with the most simple laceration and contusion, to the more severe, multiple injuries involving many organ systems. Of interest in this trauma group have been the striking increase in the number of cervical spine injuries, particularly fractures of the odontoid process of the second cervical vertebra. In the past, the neurosurgeon and the orthopedist have considered this as one of the more uncommon fractures of the cervical spine, the lower cervical spine being much more commonly involved in the typical fracture-subluxation problems.

Anatomy

Anatomically the odontoid process or dens is an upward projection of the body of the second cervical vertebra or axis. From the developmental standpoint the odontoid process represents the body of the first cervical vertebra or atlas, the anterior arch of which has an articular surface with the upward projecting odontoid process (Figure 1).

Ligaments

The lateral and posterior surfaces of the odontoid are bound quite firmly by several stout ligaments, to both the anterior arch of the atlas and to the anterior lip of the foramen magnum (Figure 2). The largest of these ligaments is the cruciform, which has no firm attachment to the odontoid itself, but only acts as a "sling" to hold the odontoid firmly against the anterior arch of C_1. The transverse portion of this cruciform ligament is the strongest segment and is attached on either side of the odontoid to the anterior arch of C_1 to form a "sling." In actuality, a synovial cavity exists between the cruciform ligament and the odontoid, which in turn allows considerable rotatory motion (but not significant anteroposterior motion) to occur at the atlanto-axial articulation. Projecting laterally and upward from the odontoid are several smaller ligaments, which serve to further bind it to the atlas and skull and which also act as check ligaments in the rotatory motion at this joint (Figure 2). Additionally, a specialized portion of the posterior longitudinal ligament, the tectorial membrane adds further support to the area.

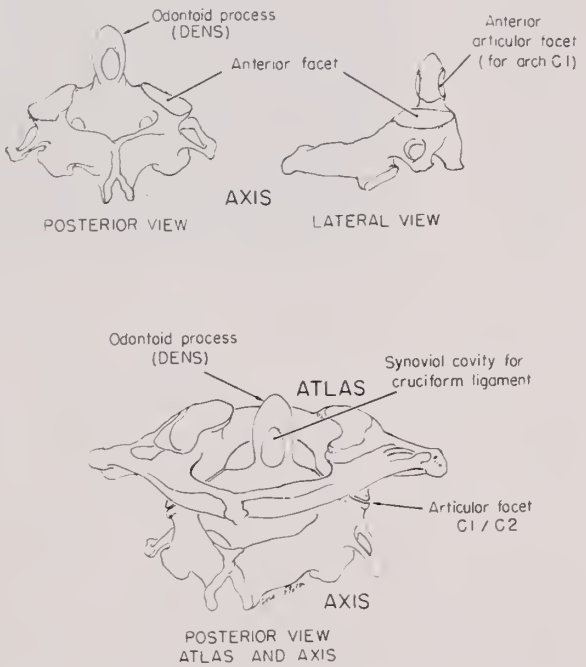


Fig. 1—Views of the atlas and axis demonstrating the odontoid process (dens) of the axis (C_2) and its articulation with the atlas (C_1). Developmentally the odontoid process represents the body of the atlas. Note the transverse plane of the atlanto-axial articulation. This allows considerable rotatory motion of this joint.

*Division of Neurosurgery, Hennepin County General Hospital and the Department of Neurosurgery, University of Minnesota Hospitals.

See editorial, page 275.

The Articulations

A second anatomic pecularity of this region relates to the atlantoaxial articulations in that they arise more anteriorly from the body and pedicles of the atlas and axis, rather than as in the usual, typical vertebra, where they arise more posteriorly at the junction of the pedicles and laminae (Figure 1). In effect then, they substitute for the usual interbody articular surface between these two adjacent vertebrae; thus in essence the typical posterior facets of both C_1 and C_2 are absent. Of more significance is the plane in which these articular surfaces are located (Figures 1 and 2). It is basically a horizontal one, rather than the usual situation in a typical vertebra where it tends to be vertical. This, of course, again allows considerable rotatory motion at the atlantoaxial joint, but also predisposes this joint to dislocations or problems of fracture-dislocation, with anteroposterior (flexion-extension) forces.

Blood Supply

It is obvious that the anatomic pecularities of this region predispose it to injury by certain types of forces; but, in addition, the anatomic uniqueness of the odontoid process predisposes it to problems of non-union, with secondary pseudoarthrosis and instability. This occurs in part because the basic blood supply of the odontoid is derived from the body of the second cervical vertebra. Obviously then, any fracture that occurs in this area disrupts the blood supply, predisposing the area to problems of non-union, especially in the more significant fracture-dislocations and most particularly when the fracture is not well reduced and adequately immobilized. As a consequence, a minor fracture through the base of the odontoid process, that is minimally displaced and not obvious in its early stages, can very readily develop subsequent non-union, with an unfortunate instability problem and the associated dangers of spinal cord compression.

Injuries

As one can deduce from the anatomy of the area, two basic types of injury are possible at the atlanto-axial articulation.

Ligamentous Injury

First is a purely ligamentous injury, where the ligaments binding the odontoid to the atlas are torn. With flexion, this will allow the atlas and skull to sublux forward on the second cervical vertebra. Of course there has to be additional ligamentous injury posteriorly and anteriorly to allow a significant forward dislocation; while a posterior dislocation of the atlas and skull in this situation is not possible because of the immobile, upward projecting odontoid process. On x-ray one typically notes, in the lateral view, a forward displacement of the atlas and occiput on C_2, especially notice-

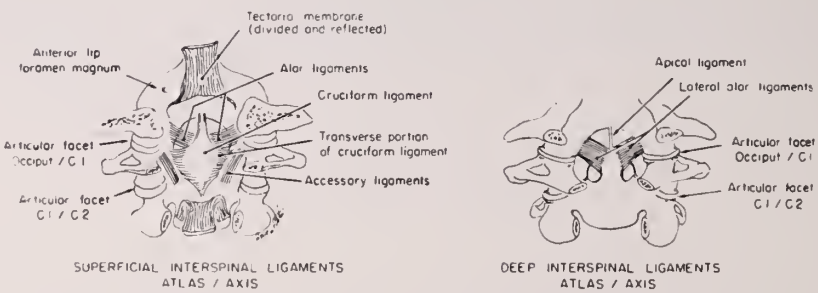


Fig. 2—Views of the superficial and deep intraspinal ligaments binding the odontoid process to the anterior arch of the atlas, as well as to the anterior portion of the foramen magnum. The posterior arches of the atlas and axis have been removed. Note that the strong cruciform ligament is not attached to the odontoid process and is separated from it by a synovial cavity. This permits the ligament to function as a "sling," firmly binding the odontoid to the atlas. As a consequence, considerable rotatory motion, but little anteroposterior motion, is allowed. Note also the reflected tectorial membrane (a specialized portion of the posterior longitudinal ligament) which lends further support to the area.

able in flexion, with a widening of the articular space between the odontoid and anterior arch of C_1 (Figure 3).

Congenital hypoplasia of the odontoid and rheumatoid spondylitis seem to predispose to this type of injury. If the dislocation is significant, compression of the spinal cord can certainly occur by the forward subluxing posterior arch of C_1. This type of injury does not seem to be particularly common.

Fractures

The more frequent injury in this area involves a fracture through the base of the odontoid (Figures 5 and 9). This allows the skull, atlas and fractured odontoid to remain together as a unit and to dislocate forward on C_2, as in the case of the ligamentous disruption. Less commonly there is an acute posterior subluxation through the fracture site. Again major bony subluxations can readily produce spinal cord compression from either an anterior or posterior direction; and obviously, significant spinal cord injury in this area is commonly fatal due to respiratory embarrassment. Fortunately, the intraspinal canal at this particular level is rather generous and allows for some minor degrees of motion and subluxation without compromising the spinal cord. It is to this group of patients that attention and early diagnosis must be particularly directed.

Clinical Cases

During the past 20 months we have had the opportunity at Hennepin County General Hospital to examine and treat some 14 patients with fractures of the odontoid process. The majority of these patients have had acute injuries, with the single most common cause having been the automobile or automobile-pedes-

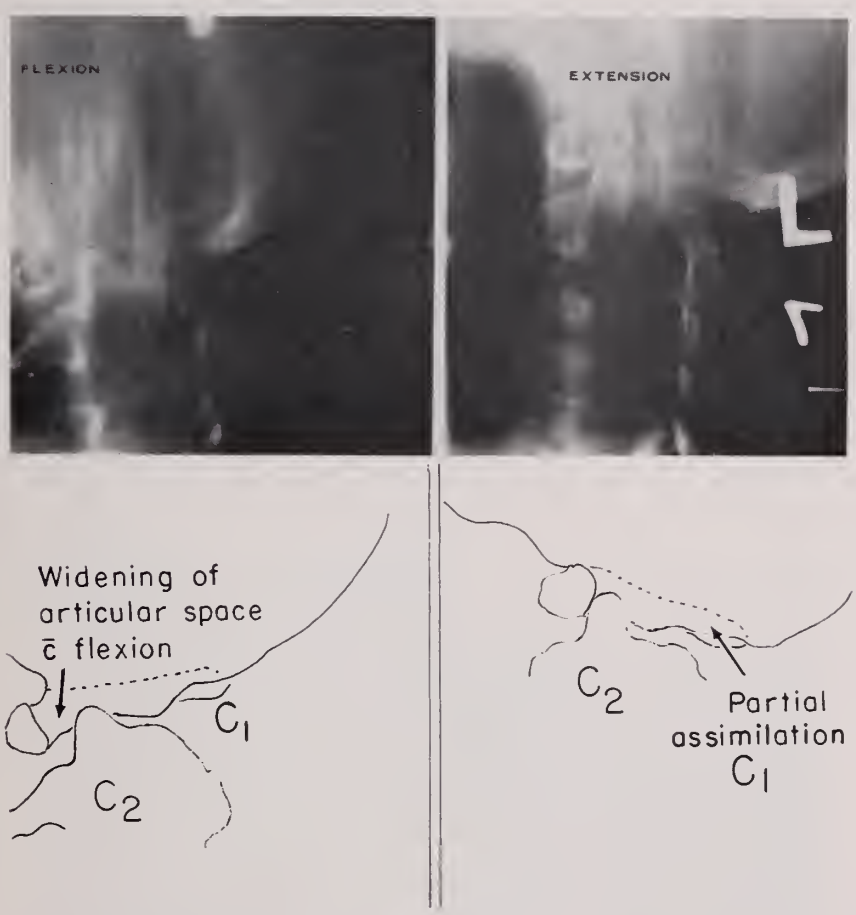


Fig. 3—Lateral flexion-extension planigrams of the upper cervical spine following an acute cervical injury. These demonstrate, in flexion, a widening of the articular space between the odontoid process and C-1. Note also the congenitally hypoplastic odontoid process and the partial assimilation of the arch of the atlas to the occiput.

trian accident. Several of the patients had old non-united odontoid fractures which were not diagnosed until the patient's neck or neurologic complaints drew attention to this area. Of interest was the lack of specific neurologic findings in the acute group of patients, who for the most part were neurologically normal, the only exception being an occasional complaint of subjective hypalgesia involving the C_2 dermatome. Uniformly these acute patients all complained of severe neck pain, which at times radiated into the C_2 dermatomal area. In general, these patients had suffered an acute flexion injury of the cervical spine and less commonly an acute hyperextension type of injury. The most common accompanying injury was that of a cerebral concussion, undoubtedly related to the impact that had produced the acute flexion-extension injury. As is routine in all cases of this nature, standard views of the cervical spine were obtained, including the standard A-P "open-mouth" odontoid view. In several of these cases the odontoid fracture was not apparent to casual examination and was demonstrable only on closely scrutinizing the x-ray films. It has been our policy in those patients where there is any clinical suspicion of a cervical fracture, to obtain repeat views, if on the initial films *all* areas of the cervical spine are not *optimally* visualized. If any further question remains, planigraphy is then carried out of any area of suspicion. The following two cases serve well to illustrate this point.

Case 1

This 57-year-old gentleman was involved in an auto-pedestrian accident in which he sustained multiple contusions and abrasions, as well as a mild cerebral concussion. When first examined he complained of pain involving the upper cervical region; consequently the standard series of x-rays of the cervical spine were then obtained (along with a routine skull series). All of these films were quite within normal limits, and all views of the cervical spine were more than satisfactory (Figure

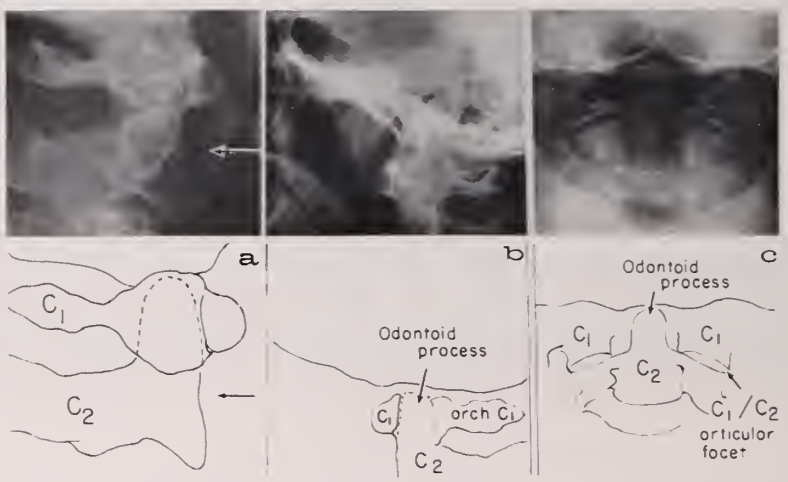


Fig. 4 (abc)—Case 1: Lateral cervical spine, lateral skull and "open mouth" A-P odontoid cervical view, demonstrating no clearcut evidence of an odontoid fracture.

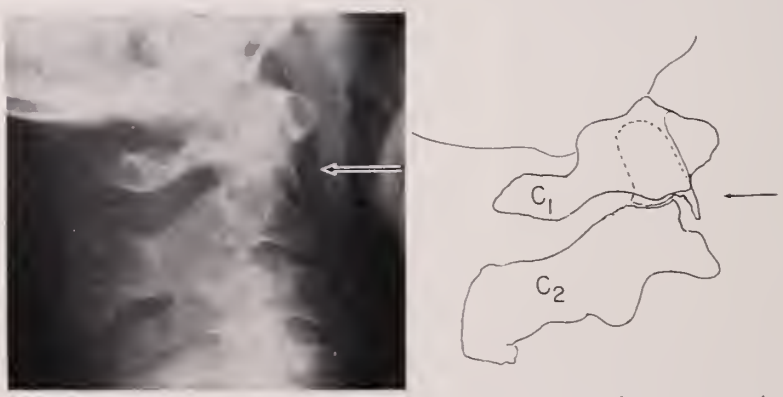


Fig. 5—Case 1: Repeat lateral cervical view, demonstrating now an obvious fracture of the odontoid process.

4). In light of the continued complaints referable to the neck region, the patient was placed in a supportive collar and further x-ray studies carried out. Again these films were rather unrewarding; nevertheless, cervical support was continued. The following day a repeat lateral film of the cervical spine was obtained, and this now demonstrated an obvious, minimally displaced fracture of the odontoid process (Figure 5). Planigraphy of the area further delineated the fracture quite adequately and appropriate therapy was then initiated. No attempt will be made in this discussion to elaborate on the various means of management of an odontoid fracture. This will be discussed in a subsequent publication.

Case 2

This 62-year-old lady suffered an injury to the cervical region in a fall down a flight of stairs, after which she noted considerable neck discomfort. She was examined and treated by a local chiropractic physician, who obtained x-rays of the area and carried out several cervical manipulations. As this resulted in no improvement in the patient's symptomatology she sought further medical aid. When examined at Hennepin County General Hospital she was neurologically intact but had considerable paravertebral muscle spasm. X-rays of the cervical spine were not definitely diagnostic, but there was a strong suggestion of a break in the bony cortex anteriorly, at the base of the odontoid process, along with very slight anterior subluxation (Figure 6). Planigraphic x-rays of the area were obtained which readily confirmed the presence of an odontoid fracture (Figure 7). Again appropriate therapy was carried out, and when last examined the patient was doing well and was symptom-free.

The diagnosis of a fracture of the odontoid process can be a difficult one and must be mainly suspected from the patient's clinical complaints, history, and findings; even with optimal x-rays of this area, one can easily overlook a nondisplaced fracture. This has prompted

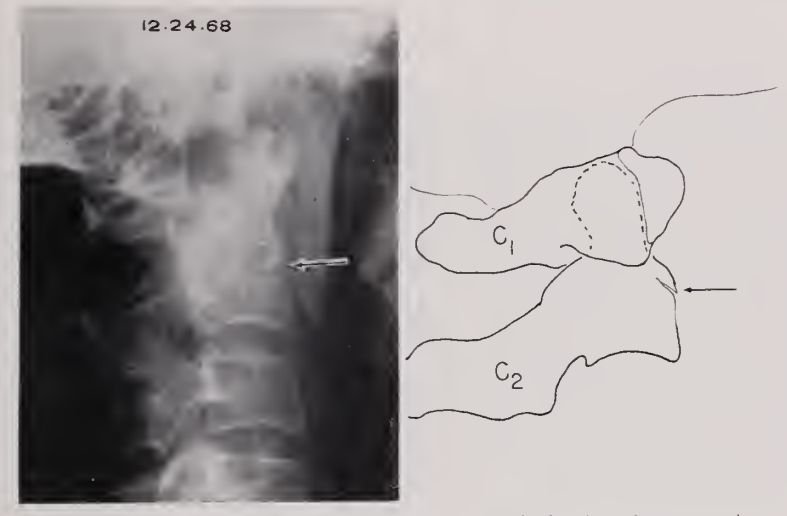


Fig. 6—Case 2: Lateral view of the upper cervical spine, demonstrating a probable break in the bony cortex anteriorly at the base of the odontoid, along with very slight anterior subluxation.

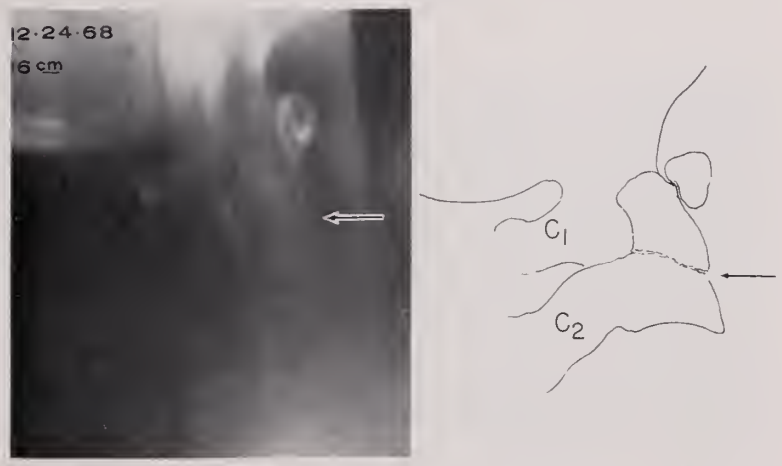


Fig. 7—Case 2: Lateral planigram, demonstrating a very obvious odontoid fracture.

us to establish a policy of repeating x-rays of the cervical spine in those patients who have persistent symptoms and to carry out planigraphy of any area of suspicion.

The fact that this fracture can be easily overlooked is exemplified in the three patients of this group who had old fractures of the odontoid, which had obviously undergone non-union with subsequent secondary instability. The exact circumstances of these three patients' earlier injuries were not known, since they were all elderly and unable to provide much past history. A review of their available old hospital records failed to indicate any type of past cervical problem. All three patients exhibited no neurologic findings which could be interpreted as being secondary to the odontoid fracture. Dynamic flexion-extension views of the cervical spine revealed considerable motion through the old fracture site in two of the three patients, and one wonders whether or not these individuals would ever have any problems related to their fracture. The third case indicates that this can be the situation.

Case 3

This 67-year-old gentleman, who was a nursing-home patient, secondary to chronic brain syndrome, was admitted to Hennepin County General Hospital with respiratory difficulty, obvious dehydration and pneumonia. Because of the patient's general debilitation, he was experiencing some difficulty in handling his pulmonary secretions and in respiratory exchange. At one point he became profoundly hypoxic and suffered a transient respiratory arrest which necessitated acute emergency intubation in order to clear his airway and assist his respirations. Following the intubation procedure and adequate oxygenation the patient immediately became more responsive; however, neurologic examination now demonstrated the presence of a quadriparesis. Attention was immediately directed to the cervical spine area, where an obvious old fracture of the



Fig. 8—Case 3: Lateral hyperextension planigram of the upper cervical spine (post mortem), demonstrating an old odontoid fracture with marked subluxation. Note that the anterior arch of C-1 (and odontoid) now lie completely posterior to the body of C-2.



Fig. 9—Case 4: Initial post-injury cervical spine x-rays, demonstrating an obvious acute odontoid fracture.

odontoid process was found, with secondary marked instability. The fracture was readily reduced with traction and further appropriate supportive therapy then carried out, but in spite of these supportive measures the patient had continued respiratory problems and expired secondary to his pneumonia.

Postmortem flexion-extension planigrams of the cervical spine revealed very marked instability at the site of the old fracture, with a particularly marked subluxation on hyperextension (Figure 8). These findings were confirmed at autopsy when, in hyperextension, the cervical cord at the C_1 - C_2 level appeared to be compressed by the fractured odontoid process and the arch of C_2. Undoubtedly this accounted for the patient's quadriparesis. An additional case again illustrates that late neurologic sequelae can develop following an odontoid fracture.

Case 4

This 58-year-old man, with a long-standing problem of chronic alcoholism, was examined in the Hennepin County General Hospital Emergency Room following a fall down an embankment. At that time he had considerable neck pain, and x-rays of the cervical spine demonstrated the presence of a modestly displaced odontoid fracture (Figure 9). Other than hypalgesia involving the C_2 dermatome the patient was neurologically normal and, despite repeated attempts at hospitalization, he steadfastly refused medical care. Further numerous attempts at follow-up were still unrewarding.

The patient was next seen some 14 months later, at which time he complained of some difficulty in the use of the right side. His neurologic findings were minimal, but definite. Cautious further x-rays of the cervical spine demonstrated the presence of a non-united odontoid fracture with considerable instability (Figure 10). At this juncture the patient was more agreeable to medical treatment and subsequently was hospitalized and appropriate operative fusion of the area carried out. When last ex-

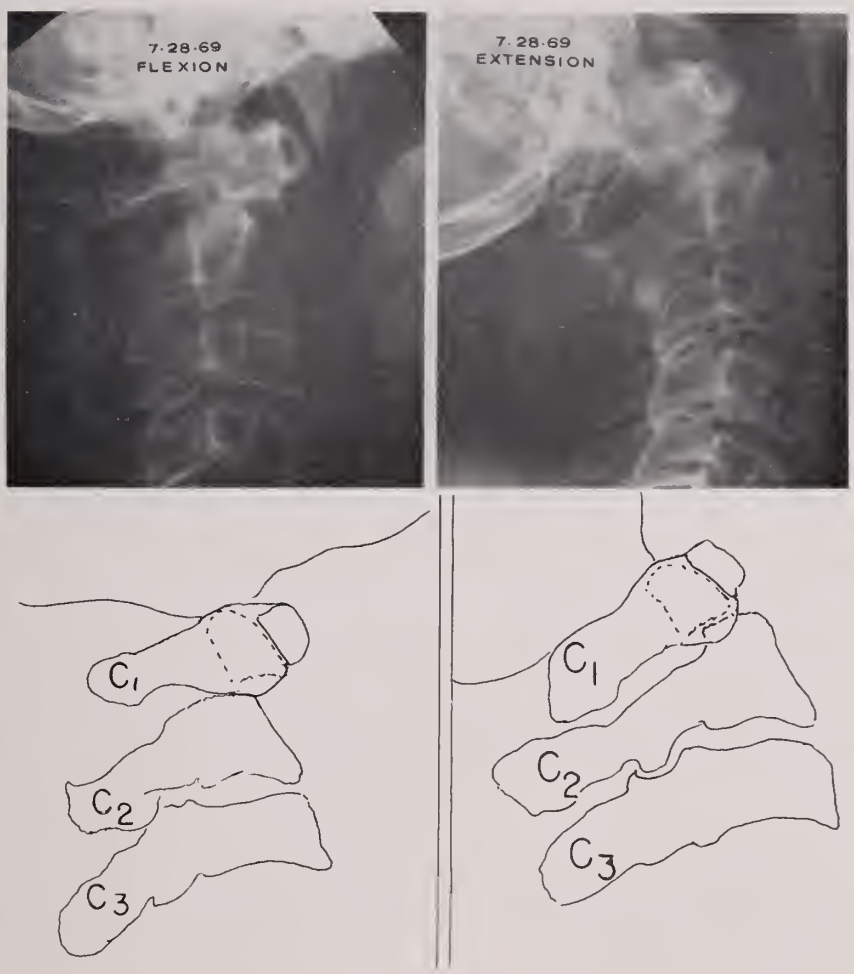


Fig. 10—Follow-up x-rays at 14 months of the patient in Case 4, who earlier had vehemently refused medical care. Note the marked instability through the old fracture site.

amined, he had returned to normal neurologically and was symptom-free.

Conclusions

Fractures of the odontoid process can be very capricious in their diagnosis. Unless one becomes suspicious that a patient may harbor a problem of this sort, minimal fractures in this location can easily be overlooked. In addition, one must continue to be ever mindful of this diagnosis, even though initial x-rays of the area may be quite unremarkable. This is particularly true where the odontoid process is not optimally visualized on the initial x-ray studies.

We have found it particularly valuable to repeat films on all patients who continue to manifest complaints referable to the cervical spine and to planigram any area of suspicion.

The early diagnosis of an odontoid fracture obviously is of paramount importance, for an overlooked fracture in this area serves only to court potential disaster.

The Scheme of Virtues*

It was about 1733 that I conceived the bold and arduous project of arriving at moral perfection. I wished to live without committing any fault at any time; I would conquer all that natural inclination, custom, or company might lead me into. As I knew, or thought I knew, what was right and wrong, I did not see why I might not always do the one and avoid the other. But I soon found that I had undertaken a task of great difficulty and I therefore contrived the following method. I included under thirteen names of virtues all that at that time occurred to me as necessary or desirable, and annexed to each a short precept, which expressed the extent which I gave to its meaning.

The names of the virtues were: Temperance, silence, order, resolution, frugality, industry, sincerity, justice, moderation, cleanliness, tranquility, chastity and humility.

My intention being to acquire the habitude of all these virtues, I determined to give a week's strict attention to each of them successively, thus going through a complete course in thirteen weeks, and four courses in a year. I had a little book, in which I allotted a page for each of the virtues; the page was ruled into days of the week, and I marked in it, by a little black spot, every fault I found by examination to have been committed respecting that virtue upon that day. My scheme of order was as follows:

5 - 8 a.m. What good shall I do this day? Rise, wash and address Powerful Goodness. Contrive day's business, and take the resolution of the day; prosecute the present study, and breakfast.

8 a.m. - 12 noon. Work.

12 - 1 p.m. Read, or overlook my accounts and dine.

2 - 6 p.m. Work.

6 - 10 p.m. Put things in their places. Supper. Music or diversion, or conversation. Examination of the day. What good have I done this day.

10 p.m. - 5 a.m. Sleep.

In truth, I found myself incorrigible with regard to order, yet I was, by the endeavor, a better and a happier man than I should have been if I had not attempted it. It may be well that my posterity should be informed that to this little artifice, with the blessing of God, their ancestor owed the constant felicity of his life.

*Benjamin Franklin (1706-1790)

Gas Gangrene Infections Related to Compound Fractures

GLEN D. NELSON, M.D.* RAMON B. GUSTILO, M.D.*
and CLAUDE R. HITCHCOCK, M.D., Ph.D.*

THE ADVENT OF HYPERBARIC oxygen therapy for gas gangrene infections has concentrated cases in a number of centers around the United States. It thus provides a unique opportunity to study a disease process which has become increasingly rare, but has certainly not disappeared. During World War I 1% of soft tissue wounds were associated with gas gangrene infections and 5% of all compound fractures were associated with gas gangrene. In the succeeding wars the incidence became progressively lower until the Korean War where the incidence was 0.1% in serious wounds. Antibiotics and more aggressive debridement and surgical procedures along with technical advances of our age certainly have contributed to the improvement in terms of reduction of numbers of cases of gas gangrene. Gas gangrene is most commonly considered as related to trauma; but we have also seen a number of cases in clean surgical wounds and even in spontaneous infections related to rectal fistulas et cetera.

Method of Study

In this paper we will deal with a group of 25 cases in which gas gangrene was associated with compound fractures. During the five-year period in which these cases were collected, over 75 cases of clostridial infections diagnosed as gas gangrene were treated at Hennepin County General Hospital. Thus it is apparent that only about one third of the cases being seen at one center are related to open fractures. The cases were all referred to the Hennepin County General Hospital from outside hospitals with the exception of one case which had only local myositis and an unusually long incubation period of 28 days.

Eight cases involved the upper extremities and 17 the lower extremities. An attempt was made to evaluate the initial treatment by review of outside hospital records and in some cases by direct conversation with the primary physician. This was not completely valid inasmuch as it is difficult to assign meaningful values, quantitatively or qualitatively, to terms such as "copious irrigation" and "thorough debridement," commonly found in operative reports. However, there were some aspects which could be specifically noted, and these included the initial use of antibiotics, type of anesthesia, manner of debridement and the use of internal fixation. Twenty-three of 25 cases were stated to have had irrigation and debridement and two, irrigation only. Three had local anesthesia and the others, regional block or general anesthesia. Twenty-two of 25 cases were treated in an operating room; the other three were puncture type wounds treated in the Outpatient Department. Only six of 25 received antibiotics initially. Internal fixation was used in six of 25 cases.

*Department of Surgery, Hennepin County General Hospital, Minneapolis, Minnesota.

Results

Type of Infection

The infections were classified as follows:

1. Localized cellulitis characterized by cellulitis of the subcutaneous tissue without muscle involvement.
2. Localized myositis, characterized by local muscle infection and necrosis but without spread or severe systemic effects.
3. Diffuse spreading myositis (true gas gangrene), characterized by a progressive muscle infection associated with crepitance secondary to gas formation and/or marked edema, with resulting necrosis and spread to adjacent muscle areas. Systemic effects are common in this category.

In our group one case was a localized cellulitis, three cases were localized myositis, and the remaining were diffuse spreading myositis or true gas gangrene.

The Infecting Organism

The infecting organism was clostridium perfringens in all but one case, and all wounds cultured at least one other pathogenic bacterium. Seven major groups of clostridial organisms are commonly described, but there are a number of additional and rare species. The best known

are: 1. Clostridium perfringens (welchii), 2. Clostridium septicum, 3. Clostridium novyi (interesting because of the absence of gas in these wounds), 4. Clostridium sporogenes, 5. Clostridium falla, 6. Clostridium histolyticum, 7. Clostridium tetani.

Numerous toxins are produced, including alpha, theta and eta. The alpha toxin is most active in terms of tissue destruction and hemolysis; other toxins affect myocardial performance, the central nervous system, liver function, et cetera, probably by interference with cell metabolism. It is important to note that other organisms, including Streptococcus, Staphylococcus and various gram-negative strains, may produce gas and cellulitis, thus mimicking gas gangrene.

It is interesting that all of our infections have been mixed, and this suggests that the clostridial organisms may be most active in a symbiotic relationship with other bacteria.

Clinical Manifestations

Clinical manifestations of gas gangrene infections include: 1. A variable incubation period which may be as short as a few hours or as long as weeks. The earliest symptoms noted in our series appeared at four hours in one case. In another, the infection was not clinically apparent for 28 days following the initial injury, albeit there were two intervening operative procedures. Our average incubation period was three days. 2. Pain (probably the earliest symptom); 3. tachycardia; 4 pyrexia; 5. shock; 6. oliguria and anuria sometimes preceded by hemoglobinuria; 7. mental deterioration (acute brain syndromes probably secondary to neurotoxin); 8. wound appearance: typical odor, color—typical bronzing, crepitance (except novyi); 9. laboratory studies—falling hemoglobin (associated with rising bilirubin and elevated plasma hemoglobin when hemolysis is occurring), elevated white blood count (although not often above 18,000 to 20,000), elevated SGOT associated with muscle necrosis; 10. x-rays—presence of gas in tissues.

Treatment

Treatment at our hospital included supportive therapy, antibiotics and debridement (including amputation when indicated), and hyperbaric oxygen therapy.

Supportive Therapy

Supportive therapy is primarily related to fluid and electrolyte balance and, of course, maintenance of major organ function. Large volumes of plasma fluid may be sequestered and must be replaced. If active hemolysis is occurring, alkalization of the urine with the use of intravenous bicarbonate should be considered to reduce hemoglobin precipitation in the renal tubules. Of course, blood transfusions are frequently required. Steroids and vasopressors may be needed if the picture of gram-negative sepsis appears.

Antibiotics

In our experience, penicillin is the drug of choice and should be administered in large intravenous doses (e.g., 3,000,000 units q4h). However, since the infections are usually mixed, a second agent to offer broad-spectrum coverage should be added, e.g., Kantrex or chloromycetin. In the case of penicillin-sensitive individuals, Keflin or tetracycline may be selected as they have demonstrated good therapeutic efficacy in clostridial infections.

Hyperbaric Oxygen

Hyperbaric oxygen therapy for gas gangrene was first reported by Boerema in Amsterdam in 1961. Bacteriologic studies by other investigators have shown that clostridial organisms produce H_2O_2 in the presence of O_2 and are then destroyed by the H_2O_2. However, the enzyme catalase causes degradation of H_2O_2, and catalase is found in significant quantities in blood and muscle tissue—precisely the site of clostridial myositis. Studies by Hill and Osterhout[3] suggest that an excess of peroxide is produced in the presence of hyperbaric oxygen, and this is the mechanism postulated by these investigators to explain their favorable experimental results in the destruction of gas gangrene organisms even in the presence of catalase.

Results

There were two deaths in 24 cases directly related to the clostridial infection. A third death was felt not to be associated with infection inasmuch as the gas gangrene infec-

tion had been absent for 30 days when the patient succumbed to peritonitis and general sepsis following surgery for a perforated duodenal ulcer. Thirteen of 25 cases required amputations, a number of which had been accomplished prior to transfer to our hospital. We did not resort to amputation to control the infection, but rather to remove completely nonviable or non-functional limbs. In this series progression of infection could be controlled by debridement, hyperbaric oxygen, antibiotics, et cetera, in all cases. In other words, we did not have to amputate proximally to stop spreading infection. In several cases we were able to control progression of infection following amputation elsewhere.

Discussion

Initial Treatment

Since the vast majority of our cases have been associated with extensive trauma, and with our knowledge of the clostridial organism's behavior, it is logical to assume that nonviable tissue is probably present in most, if not all, cases of the type that develop clostridial myositis. The need for complete irrigation and debridement in initial therapy is apparent. Delays in initiation of treatment must be avoided. A fairly long delay between injury and initial treatment was noted in several of our cases and certainly could be contributory to the establishment of infection. Prompt administration of antibiotics in adequate doses and of appropriate type in most compound fractures would seem indicated, particularly in view of the fact that only six of 25 of our cases that developed clostridial infections received antibiotics initially. Also in some of those initially treated with antibiotics the dose was inadequate and the type of antibiotic inappropriate. It is our policy at Hennepin County General Hospital to use antibiotics from the time that we first see compound fractures. We have not noted any gas gangrene infections in a series of 707 compound fractures seen from 1955 to 1968 at our institution and treated with adequate irrigation, debridement and appropriate antibiotics in adequate doses. The physician must be alert to the potential for clostridial infection in certain wounds so that infection can be recognized and treated as early as possible, since failure to treat early can certainly lead to the loss of additional tissue.

Once infection is established, the failure of response to usual means, including antibiotics and adequate debridement, or the appearance of systemic toxins, suggests the need for a trial of hyperbaric oxygen therapy.

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A Reason

I wanted to be a doctor that I might be able to work without having to talk. For years I had been giving myself out in words, and it was with joy that I had followed the calling of theological teacher and of preacher. But this new form of activity I could not represent to myself as talking about the religion of love, but only as an actual putting of it into practice.*

*Albert Schweitzer, as quoted in A Mirror up to Medicine by A. C. Corcoran, M.D., 1961.

From The Doctor's Dream*

I had a dream, and in that dream
I thought that I had passed
Into that realm of blissful rest
That doctors reach at last.

I dreamed of all the ups and downs
Of thirty years of practice,
That brought with many a scented rose,
Its compensating cactus.

About the doctors and their bills,
The good and bad we did,
The lives our skill so often saved,
Mistakes the earth had hid.

And thus I dreamt that round me stood
The victims of disease,
The patients I had failed to cure,
Though some had paid my fees.

One said, "It is a happy place,
My bliss is unalloyed;
Through your mistakes just ten years more
Of Heaven I have enjoyed."

Another made this queer complaint;
"I'm prematurely sent:
The bungling doctors got me here
Before development."

I here got shaky in my shoes,
And asked if they'd attack us,
And raise a rumpus in these courts,
With questions of malpractice.

"Oh, no!" he said, "there's no redress,
No righting this affliction:
For courts are not in session here
For want of jurisdiction.

"And if they were, in our behalf
We must ourselves appear;
A first-class lawyer can't be had,
I never found one here."

---

*William Snowden Battles (1827-1895) studied medicine under Dr. Timothy Hunt Baker at Millbrook, Ohio, for four years. He received the degree Doctor of Medicine in 1852 at Starling Medical College in Columbus, Ohio. His contributions to medical literature are studies on scarlatina, ergot and alcohol. His research and writing brought him the vice-presidency of the Ohio State Medical Society in 1886 and other honors.

Traumatic Hip Dislocation*

Treatment and Results

CHARLES H. MILLER, III, M.D.,† RAMON GUSTILO, M.D.†
and JOSEPH TAMBORNINO, M.D.†

THE SUBJECT OF HIP dislocation can no longer be considered new. It has been the topic of many scholarly reviews, and to attempt to outdo or even equal some of them would be monumental if not impossible in a relatively small metropolitan area. Neither, however, can hip dislocation be considered "old hat," for it is only by alert, aggressive management that the notorious complications of this rare injury can be minimized. The nature of Hennepin County General Hospital as a receiving hospital during the years covered by this report (approximately 1955 - 1969), often transferring patients to outlying hospitals after initial therapy, makes the results of this study a combination of initial receiving hospital reduction and the private physician's long-term therapy.

The 517 patients reported by Brav[1] from the U. S. Army must serve as the most prestigious recent work. It is upon his classification and other frames of reference that the present study will be most closely based. Stewart and Milford[6] of the Campbell Clinic in Memphis reported an excellent follow-up series of 128 patients. Other outstanding reports include: Thompson and Epstein (L. A. County) 294 cases;[2] Armstrong (Royal Air Force) 101 cases;[3] and Urist (European Theater of Operation) 27 cases.[4]

Anatomy

A brief anatomic review of the blood supply to the femoral head reminds us that the retinacular vessels are derived from the circumflex femoral arteries, and the vessels of the ligamentum teres are derived from a branch of the obturator artery which can communicate with the femorally derived vessels. Ligamentum teres vessels do not always pass into the head; thus the superior retinacular group, the lateral epiphyseal arteries, provide the most important arterial supply to the head.

Etiology

Automobile and motor bike accidents along with a few falls from excessive heights or with just the proper amount of flexion and angulation account for almost all of the recorded fracture-dislocations in recent series. Trauma which approximates the knee and pelvis with the necessary force can produce a posterior dislocation, whereas anterior dislocations are the result of abduction with or without external rotation. The capsule and ligamentum teres are always torn, with subsequent damage to the blood supply. Posterior protrusion of the head of the femur through the capsule may injure short rotator muscles and the sciatic nerve, while anterior dislocations traumatize the adductor and obturator internus muscles.

Classification

Brav's[1] classification has been utilized in this report for purposes of comparison and simplicity.

TABLE I
Classification of Hip Dislocations[1]

Type A —Anterior dislocation.
Type I —Posterior dislocation without fracture.
Type II —Posterior dislocation with fracture of the posterior lip of the acetabulum.
Type III—Posterior dislocation with fracture through the acetabulum or the femoral head.
Type C —Central.

It may easily be argued that this classifica-

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tion lacks enough sophistication to merit general acceptance. Indeed, reclassification and revision of previously recorded cases may yet provide information which will afford the ultimate in reviews (like the present report) with a goal of minimal long-term complications and sequelae, the results of properly selected cases for open or closed reduction, and ideal periods of non-weight bearing.

Diagnosis

A high index of suspicion, close observation, and physical examination coupled with adequate pelvic and lateral hip films of patients involved in major accidents will reward the physician with a proper diagnosis. The so-called "gull-wing sign" proves the value of the lateral view of the pelvis in fracture-dislocation of the acetabular rim and posterior dislocation of the femoral head, as the joint may appear normal in the anteroposterior position, but the lateral x-ray will show the femoral head and posterior acetabular rim posteriorly displaced.[5]

Campbell in 1936 suggested watching any disturbance in Shenton's line or narrowing in the superior joint space. Subluxation, bone chips, or loose fragments in the acetabulum are observed on a combination of anteroposterior and lateral films or stereo views. Occasional dislocated femoral head injuries will be found with fracture of the shaft of the femur, prompting need for roentgen examination of the entire pelvis and femur.

Treatment

Although most authorities agree on the importance of immediate reduction, Stewart and Milford[6] stated that with sufficient traction surgery can be delayed for a week to 10 days without adverse effects.[7]

Stewart[8] found the Stimson method to be the best, although he felt that it was rarely used, since there was no audible pop which could be heard as in other reductions. It is noteworthy that fracture may occur to the neck or femoral shaft during an attempt to obtain the closed reduction. Primary arthrodesis or cup arthroplasty is rarely indicated.[1,8] The early recognition and closed reduction without undue force is most important. Good x-rays including pre- and postoperative reduction films, are a *sine qua non* of good management. When closed reduction is unsuccessful or bone fragments are seen in the joint space, early open reduction is indicated.

The following schedule outlines Brav's[1] therapeutic activity regimen.

Class	Traction	Hip Motion	Weight Bearing
A and I	3 Weeks	3 Weeks	12 Weeks
II and III	6 Weeks	12-12 Weeks	16+ Weeks

Return to activity: A and I — 14 weeks; II and III — 14 to 18 weeks.

One author[6] stated that a patient believed his relatively early and vigorous active exercise of the hip was responsible for successful outcome. It is interesting to note that exactly the same unsolicited remark was made by one of our patients who had a completely successful recovery in the current series.

Complications

The long list of complications from this major trauma include fracture of the surgical neck during reduction; fatigue fracture of the femoral neck after successful open reduction; avascular necrosis; and mechanical incongruity and traumatic arthritis. Also myositis ossificans of the short rotators, periarticular calcification, peroneal nerve paralysis, surgical infection and spontaneous fibrosis or bony anklyosis.[8]

The onset of avascular necrosis is usually considered to be approximately 17 to 18 months in non-surgical cases; however, cases as early as six months and as late as five years have been reported.[1] Etiologic factors include interruption of the blood supply; thrombosis of the innerosseous vessels of the Haversian system (similar to Cassion's disease) and a "shock and counter shock (counter force)" of trauma theory with intracellular changes. Brav[1] reports that avascular necrosis was not visible on x-ray in 33 percent of 69 cases for at least six months and there was no correlation to time of weight bearing with the functional results. Nor did the clinical results always parallel x-ray changes.

The large Army series[1] reported a 1.5 percent redislocation. The 55 patients in the current series had one redislocation. Another large series[6] reports arthritic changes in 48

percent of 90 patients who had had closed reductions. Sciatic nerve involvement was quoted to be 13.3 percent, with only two cases revealing myositis ossificans.

Follow-Up

A rule of thumb for clinical follow-up includes examination every three months for at least two years. Stewart[6] felt that significant follow-up could not be obtained before 18 to 24 months.

Results

The two prime factors which dominate the literature reviewed as far as the end clinical results of treatment are: (1) the severity of the accident and (2) the time before reduction. The full significance of unsupported weight bearing, and the use of weight-bearing braces is still unknown. Although age has little influence on the end results, it would be misleading to assume that a severe injury in the nature of hip dislocation would not affect an older patient more disadvantageously than a similarly injured youth.

Although we failed to see any sciatic nerve injury immediately after reduction or in our 26 documented follow-ups, the literature reports from 10 to 16 percent sciatic nerve injuries in large series.

Material

This study includes all of the hip dislocations and hip fracture-dislocations initially treated and/or admitted to the Hennepin County General Hospital (Minneapolis General Hospital) from January 1954 to January 1969. Fifty-five cases were recorded with 34 follow-ups of one and one-half to 15 years, including seven deceased. The nature of this county hospital as a receiving hospital enables transfer of previously acutely injured patients at a satisfactory time subsequent to initial therapy. Consequently a majority of these patients were transferred approximately six weeks after injury to their private physician's care, and our satisfactory follow-up is due in large part to the cooperation of the Twin City medical community.

Patients' ages ranged from 16 to 77 (children were not included).

Age Range	Female	Male
16-20	1	10
21-30	4	14
31-40	1	9
41-50	1	4
51-60	1	3
61-70	2	3
71-up	1	1
	11	44

Obviously, young males from the age of 16 to 40 made up the majority of injuries. The right hip was affected 30 times; the left, 23; and there were two central dislocations.

Etiology

Predictably the causes of these major injuries fall into the four major categories: (1) auto accidents 42; (2) motor bike accidents 5; (3) falls 6; and (4) other 2. It is our general impression that motor bike injuries have begun to decrease in number in recent months.

Breakdown of the 55 cases within the previously described classification follows:

Class	Over-all	Follow-up
I	24	13
II	12	5
III	12	6
Central	3	2
Anterior	4	1

Many have stressed that hip dislocation is a major fracture emergency and that long-term results bear an inverse relationship to the length of time between injury and reduction. Records of 38 patients in this series provided sufficient information to determine that an average of 4.8 hours were spent in transportation, examination, evaluation, and finally reduction. (The Army series reported an average of 6.6 hours for 469 dislocations.)

Of the 27 patients who were questioned, 19 also reported for physical examination and follow-up x-rays. Twenty-five of the 27 were treated by closed reduction and two by open reduction following unsuccessful closed manipulation; one case underwent arthrodesis a year later.

Results

Over-all, our clinical impression including physical examination and x-ray of 19 patients includes nine excellent results, six good, four

fair, and none poor (Table 2). Eight other patients submitted answers to a questionnaire, adding two excellent results, one good, and five fair. Clinical and roentgenographic criteria for evaluating results are drawn from Brav[1] (Tables 3 and 4).

It would be erroneous to draw specific conclusions regarding clinical results with different methods of treatment from our small series, specifically length of time for non-weight bearing. In general, the patients with excellent results had been placed on an activity regimen similar to that previously mentioned. It is interesting to note that 10 long-term follow-ups with excellent clinical results were in a non-weight bearing attitude for an average of 15 weeks, while six patients with fair to poor results began to bear weight at an average of 10 weeks. In the large Army series Brav[1] found that weight-bearing protection added nothing to clinically improve results after the initial four months.

Case Reports

In three cases there was x-ray evidence of fair or poor results:

TABLE 2

Sex/ Age	Type	Delay Hours	Etiology	Assoc. Fractures	Re-duction	Total N.W. Bearing	Follow-up (years)	X-Ray Evalu-ation	Clinical Evalu-ation	Pa-tient's Evalu-ation	Com-plica-tions
M21	IL	UNK	AA	Yes	C	12	8	E	E	E	N
M25	IIIL	8	AA	No	C	9	14	P	F	G*	P
M25	IR	4	AA	No	C	12	2	E	E	E	N
M21	AL	2	F	No	C	16	12	E	E	E	N
M17	IR	4	AA	Yes	O	10	1½	F	F	F	P
M19	IL	<12	AA	No	C	6 Mo 1WBB	10	E	E	E	N
M39	IIIL	UNK	MB	Yes	C	22	10	E	F	E	N
F20	IL	4	MB	No	C	18	2	G	G	G	N
F24	C	UNK	AA	No	C	UNK	2		E	E	N
M17	IIIR	6	AA	Yes	C	12	9	E	E	E	N
M20	IIR	6	MB	Yes	C	17	2	G	G	E	limp
M17	IIIL	6	AA	Yes	O	14	15	F	G	E	N
M16	IR	UNK	AA	Yes	C	13	1½	o.k.	E	E	†
M23	IIIL	UNK	AA	Yes	C	12	3	G	G	G	N
M16	IR	3	MB	Yes	C	6	5	E	F	G	Yes
F21	IIR	4	AA	Yes	C	20	5	E	E	E	N
M18	IIIR	UNK	AA	Yes	C	26	1½	VA. o.k.	E	E	N
M41	IIR	1	AA	Yes	C	17	2	G	G	E	N
M20	IL	3	AA	No	C	25	4	E	G	G	N
F60	IIR	4	AA	No	C	10	12	none	F	G	N
M35	IL	3	F	No	C	6 est.	11	none	F	F	N
M53	IR	5	AA	Yes	C	12	9	none	E	E	N
M60	IR	4	AA	Yes	C	10	9	none	F	F	N
M30	IR	4	AA	Yes	C	16	11	none	E	E	N
M27	IL	4	UNK	No	C	12	1½	none	G	G	N
F44	IIL	2½	AA	Yes	C	UNK	2	none	F	G	N
M56	C	UNK	AA	Yes	C	UNK	9	none	F	F	Ar

Footnotes:
N—None
P—Pending
1 WBB—15 had WBB 6 mos.
†Redislocation
*Originally told he'd never walk.
UNK—Unknown
None—X-ray not performed
Ar—Arthrodesis 1963

Type: See other table for classification used
Delay: Hours after injury that reduction was accomplished
Etiology: Auto Accident; Motor Bike; Fall; Other
Reduction: Open; Closed
X-Ray Evaluation: See accompanying table
Clinical Evaluation: See accompanying table

TABLE 3

Clinical Criteria for Evaluation Results

Excellent:

All of the Following

1. No Pain.
2. Full Range of Hip Motion.
3. No Limp.

X. No Roentgenographic Evidence of Progressive Changes.

Fair:

Any One or More of the Following

1. Pain, But Not Disabling.
2. Limited Motion of Hip. No Adduction Deformity.
3. Moderate Limp.

X. Moderately Severe Roentgenographic Changes.

Good:

1. No Pain.
2. Free Motion (75 percent of normal hip).
3. No More Than a Slight Limp.

X. Minimal Roentgenographic Changes.

Poor:

Any One or More of the Following

1. Disabling Pain.
2. Marked Limitation of Motion or Adduction Deformity.
3. Redislocation.

X. Progressive Roentgenographic Changes.

TABLE 4

Roentgenographic Criteria for Evaluating Results

Excellent (Normal)

All of the Following:

1. Normal Relationship Between Head and Acetabulum.
2. Normal Articular Cartilaginous Space.
3. Normal Density, Head of Femur.
4. No Spur Formation.
5. No Calcification in Capsule.

Fair (Moderate Changes)

1. Normal Relationship Between Head and Acetabulum.

Any One or More of the Following:

2. Moderate Narrowing of Cartilaginous Space.
3. Mottling of Head, Areas of Sclerosis, and Decreased Density.
4. Moderate Spur Formation.
5. Moderate to Severe Capsular Calcification.
6. Depression of Subchondral Cortex of the Femoral Head.

Good (Minimal Changes)

1. Normal Relationship Between Head and Acetabulum.
2. Minimal Narrowing of Cartilaginous Space.
3. Minimal De-ossification.
4. Minimal Spur Formation.
5. Minimal Capsular Calcification.

Poor (Severe Changes)

1. Almost Complete Obliteration of Cartilaginous Space.
2. Relative Increase in Density of Femoral Head.
3. Subchondral Cyst Formation.
4. Formation of Sequestrae.
5. Gross Deformity of Femoral Head.
5. Severe Spur Formation.
7. Acetabular Sclerosis.

Case 1

A 17-year-old white male was the sole occupant of a car involved in a head-on collision with another car on March 18, 1957. He suffered a concomitant femoral fracture which was treated with an intermedullary rod at the same time that an open reduction of the hip dislocation and screw fixation of the acetabular ring were performed. The rod was removed two years later. A thirteen-year follow-up physical examination was unremarkable, although his x-ray shows moderate narrowing of the cartilaginous space and some mottling of the head with areas of sclerosis and decreased density. The patient claims his left hip to be asymptomatic (Figures 1 and 2).

Case 2

A 25-year-old white male was involved in an auto accident on April 1, 1955. His injury was reduced by closed reduction and he was kept in a non-weight at-



Fig. 1—Thirteen-year follow-up of injury to 17-year-old male.

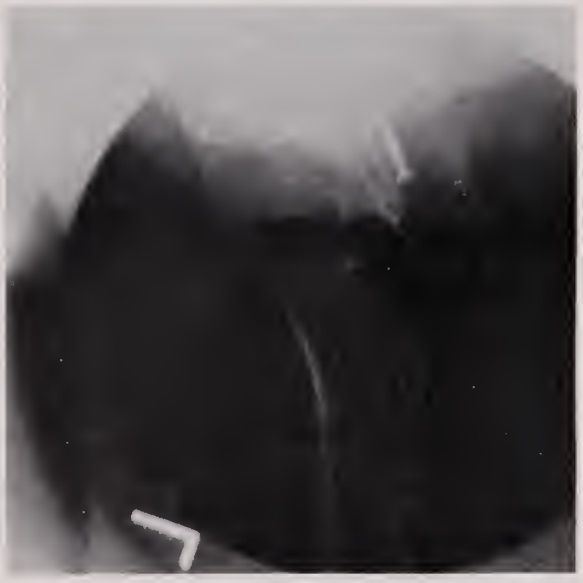


Fig. 2—Case 1 follow-up.

titude approximately nine weeks. He now has occasional pain and walks with a moderate limp: a serious complication in his position as a mail carrier (Figures 3 and 4). The patient considers his results "excellent" despite the pain and limp—probably because he was originally told that he would never walk again.



Fig. 3—Fourteen-year follow-up of injury to 25-year-old male.



Fig. 4—Case 2 follow-up.

Case 3

A 17-year-old white male was thrown from a car on May 5, 1968, suffering a fractured pelvis and simple posterior dislocation of the left leg. He was released in four weeks, claims to have stayed in a nonweight bearing attitude for another four weeks, but failed to attend clinic in follow-up for about three months. At that time he was asymptomatic, but at 18 months his x-rays show moderate narrowing of the cartilaginous space and mottling of the head. He has recently complained of increased hip pain and a limp (Figures 5, 6, and 7).



Fig. 5—Eighteen-month follow-up of injury to 17-year old male.



Fig. 6—Case 3. One-year follow-up.



Fig. 7—Case 3. Fourteen-month follow-up.

What's New

While we agreed that hip dislocation can no longer be considered new, in recent years several investigators have pursued methods of ascertaining the vascularity of bone, specifically the viability of the head of the femur.[9,10,11,12] There is currently no method available for clinical use by which a surgeon can dependably predict the development of avascular necrosis. In 1950 Tucker injected radioactive phosphorus (p^{22}) and used biopsy specimen radioactivity ratios of the head and greater trochanter to determine bone tissue viability which is dependent on the blood supply. The amount of radioactive phosphorus is felt to be an indication of viability of the bone. Clearance rates of injected radio sodium Na^{24} have been used both experimentally and in a few clinical cases by Lang and Ferguson in Pittsburgh with some success.

An instrument for the measurement of oxygen tension in bone, a transistorized polarimeter, measures availability of oxygen to the tissues involved, specifically to the femoral head or neck; but extensive statistical evaluation is not yet available.

Summary

As stated before, the relatively small series here presented does not lend to valid statistical analysis. Results are generally favorable in 18 of 26 cases. To date three possible cases of avascular necrosis are documented roentgenologically. One redislocation was reported, but no reduction fractures, myositis ossificans, peroneal nerve involvement, infection, or bony ankylosis have been identified. Results appear favorable when compared with larger series.

Methods of Closed Reduction

Allis' method *(Flexion, Traction, Patient Supine)* (Figure 8) is primarily that of traction and counter traction of the flexed thigh against the pelvis. The patient is placed on his back, the pelvis held down firmly by pressure over the iliac crests by an assistant or by a strap; the thigh and leg are flexed at right angles, and then strong continuous traction is made on the thigh grasped just above the knee. Bohler modified this method by using a towel applied around the thigh above the knee and then tied around the operator's neck. From a bending position the operator exerts a strong upward pull by straightening his back. At the same time downward pressure is exerted on the foot in order to produce leverage over the surgeon's knee which is placed in the popliteal region of the patient. Bohler reported complete success with this method. Gentle manipulation to disengage the head should be carried out; adduction and internal rotation should be increased.



Fig. 8—Allis' method.

The method of Bigelow *(Flexion, Traction, Circumduction)* (Figures 9 and 10) is more dangerous for soft tissue injuries inasmuch as it is essentially manipulative in character. The pelvis is immobilized and the thigh is rotated internally adducted and flexed on the abdomen. In this position traction is exerted on the thigh in an upward direction. Then the limb is slowly circumducted, that is, swept out into abduction and then into extension. As it is abducted it is externally rotated. This maneuver relaxes the Y ligament and brings the head



Fig. 9—Bigelow method—first step.

down to the level of the tear in the capsule. In this position traction pulls the head up on the posterior rim of the acetabulum; then abduction and external rotation pry it forward into the acetabulum.



Fig. 10—Bigelow method—second step.

The Stimson method *(Patient prone, hip flexed over end of table, traction and rocking)* (Figure 11) is probably the least traumatizing (and least dramatic). The patient is placed on the table in the prone position projecting over the end and allowing the affected thigh to hang down, the other thigh supported by an assistant. In this position gentle downward traction with slight rotation and rocking will usually effect reduction.

Anterior dislocations are reduced by Allis' method as follows. The thigh is flexed slightly and the abduction deformity and external rotation are increased; then direct traction is inserted on the thigh. These maneuvers lift the head away from the pelvis; then with traction maintained the thigh is gently adducted and internally rotated to bring the head over the rim and into the acetabulum.

References may be secured from the author or the reprints.



Fig. 11—Stimson method.

Discussion

Discusser: Joseph M. Tambornino, M.D., Attending Physician, Orthopedic and Fracture Divisions, Hennepin County General Hospital.

Dr. Miller has done a fine job of reviewing the literature in regard to hip dislocation. The series here at General is, of course, difficult to follow because of the transient character of the patient population. One surprising thing is what appears to be a relatively small number of cases (55 traumatic dislocations of the hip in 15 years).

Regarding classification of dislocation and fracture-dislocation of the hip, the method used by Brav seems to be workable, logical, and related to the prognosis.

The statement that Stewart and Milford felt that surgery could be delayed for a week to 10 days without adverse effects referred to open reduction for the fracture of the acetabulum and was not intended to imply that one could delay reduction of the dislocation. It is rather generally accepted that early reduction of the dislocation is the single most important factor in avoiding the complication of ischemic necrosis.

It should also be emphasized that this injury in a child is a much different problem with a much better prognosis, although the paper is correct in stating that among adults age has little influence on the end results.

I would like to thank Dr. Miller for an interesting review of the literature regarding this problem and his careful survey of the patients available for follow-up study.

When true friends meet in adverse hour, 'tis like a sunbeam through a shower.
—Sir Walter Scott.

148 Femoral Shaft Fractures in 144 Patients

An Analysis

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THE MANAGEMENT OF FEMORAL SHAFT fractures presents a problem to the surgeon whether the treatment will be by skeletal traction and cast or open reduction and intramedullary nailing. Intramedullary nailing of femoral shaft fractures was popularized in 1940 by Kuntscher.[3,11,12,13] Since then, several reports have advocated open reduction and intramedullary nailing as the treatment of choice for femoral shaft fractures.[1,2,4,5,14,16,18,19,22] The complications,[17] however, inherent in open reduction and intramedullary nailing (such as infection and technical difficulties) lead many surgeons to prefer skeletal traction.[8] This is a comparative study of femoral shaft fractures treated by open reduction and internal fixation versus those treated with skeletal traction and cast.

Materials

The series comprised 148 femoral shaft fractures in 144 patients from 1953 through 1967 at Hennepin County General Hospital and Methodist Hospital, Minneapolis, that could have been treated either by open reduction and internal fixation or by conservative management. The choice of treatment at Hennepin County General Hospital was decided by the chief resident in charge of the fracture service with approval of the consultant, and at Methodist Hospital by the private orthopedic surgeon.

Of the entire series, 51 patients were treated by skeletal traction and spica cast. Eighty patients were managed by open reduction and intramedullary nailing and thirteen by open reduction and a long side plate.

The ages of the patients treated by traction ranged from 16-62 years with an average age of 30.8 years. The average age of patients treated by open reduction was 31.9 years with an age range of 16-67 years. The ratio of male to female was 4 to 1.

These 144 patients have been followed for at least one year and a maximum of 15 years. More cases were treated at Hennepin County General Hospital but were omitted because of short follow-up, or the patient was transferred to his private physician or died in less than five days from multiple trauma. Car accidents comprise over 75% of the entire series.

Types and Location of the Fractures

There appears to be no difference between the type of fractures treated by traction and those treated by intramedullary nailing. The fractures were also classified according to their anatomical location (Table 1).

TABLE 1
Location and Type of Fractures

	Percent Traction	Percent Internal Fixation
Transverse	33.0	37
Oblique	33.0	25
Segmental	5.5	1
Comminuted	28.5	37
Open	16.6	10
Upper 1/3	17.0	33
Middle 1/3	71.0	64
Lower 1/3	12.0	3

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Methods of Treatment

Conservative Management

Skeletal traction is accomplished by insertion of a Steinman pin at the proximal tibia under local anesthesia. Then the leg is placed on a Thomas splint with a Pearson attachment, or a short leg cast is applied incorporating the pin for traction and a sling under the thigh. Initially, satisfactory alignment is obtained by 20-30 pounds of traction for three to four days. Following this, the alignment is maintained with about 10 pounds of weight. X-rays are taken frequently to ascertain the reduction position. The total x-rays taken of femoral shaft fracture until the patient leaves the hospital in a spica cast average 14 sets of anteroposterior and lateral projections compared to five sets for those treated by open reduction and nailing.

Operative Management

The patient is maintained in skin or skeletal traction to maintain good position and adequate length until surgery at 10-14 days after the injury. All intramedullary nailing was done by the open method using a variety of nails including Kuntscher, Hansen Street and Schneider nails. The Schneider nail has been used exclusively during the last three years[18] because the operative technique is easier, there is less dissection and a more stable fixation is obtained.

Postoperative Care

The patient is returned to the fracture bed without any form of external immobilization or traction. The day following surgery quadriceps exercises and foot and ankle motion are started. When the patient is able to lift his leg off the bed, he is allowed out of bed to start crutch walking, usually between 10-14 days. When crutch walking is first started the patient begins with toe touching and then gradually goes to partial weight bearing. He is followed at monthly intervals for range of motion and for x-rays.

Results

Hospital Stay

The average hospital stay of a patient treated in traction at Hennepin County General Hospital was 125 days and 103 days at Methodist Hospital. Patients were in traction for an average of 70 days at Hennepin County General Hospital and 60 days at Methodist Hospital. They were then placed in spica cast for three to four months. After removal of the spica cast the majority of these patients were admitted to the hospital for two weeks. A physical therapy program was then initiated to regain knee motion and quadricep muscle strength. A crutch walking program with partial to progressive weight bearing was also begun.

The average hospital stay for patients treated with intramedullary nailing was 32 days at Hennepin County General Hospital and 22 days at Methodist Hospital, or about one-fourth of the time of those patients treated without surgery.

TABLE 2
Average Hospital Stay

Method of Treatment	HCGH Days	Methodist Hospital Days
Traction	125	103.0
Open Reduction and Internal Fixation	32	22.9

Weight Bearing

The average time for patients treated by open reduction and internal fixation to bear full weight on a fractured femur is 18 weeks, while those treated with skeletal traction and cast is 39 weeks.

The rate of healing by roentgenographic criteria appears to be the same, but the incidence of non-union or delayed union for femoral shaft fracture treated by conservative management is 29.4% compared to 5% for those fractures treated by open reduction and intramedullary nailing.

Complications (Table 3)

The most dreadful complication following open reduction and intramedullary nailing or plating of femoral shaft fracture is infection. Following surgery, there was an infection rate of 3.7% with intramedullary nailing and 15.7% with plating. Of the five cases in which infection occurred after nailing, one resulted in hip disarticulation and four cases developed persistent chronic draining sinus. All these cases

were from Hennepin County General Hospital. The two patients that developed infection following plating were from Methodist Hospital. Both cases had very prolonged surgical procedures and had delayed healing and recurrent drainage secondary to chronic osteomyelitis.

The greatest complication following conservative management is non-union 29.4%. Other complications are tabulated in Table 3.

TABLE 3
Major Complications

	Percent Traction and Spica	Percent Open Reduction and Internal Fixation
Nonunion	29.4	5.0
Infection	0.0	6.4
Refracture	10.0	0.9
Pulmonary Emboli	6.0	3.2
Fat Emboli	7.8	6.4
Pneumonia	12.0	2.0
Bursitis	0.0	8.9
Skin Ulcer	10.0	0.0
Death	6.0	2.2

Discussion

Risk of Infection

Whenever a femoral shaft fracture is suitable for intramedullary nailing, the question is asked whether the risk of infection is worth taking. The reports from various authors of the rate of infection following intramedullary nailing ranges from 1-11%.[5,6,7,8,13,14,15,17,20,21] In our series, the rate of infection was 3.6% following intramedullary nailing and two out of 13 following plating. The latter represent too small a number of patients to be significant. It is a mistake to do primary internal fixation of any open fractures unless it is absolutely necessary because of neurovascular complications. In open fractures that are treated with primary nailing the infection rate is three times as high as those treated with secondary nailing.

Delay Elective Surgery

At the present time an open fracture is irrigated with copious amounts of saline and primary closure is done with or without a drain. Most of these patients are placed on Ampicillin and Oxacillin[10] for two weeks. In two to three weeks the femur is nailed and treated as an elective procedure for a closed fracture. Before 1965, many open fractures were treated with primary intramedullary rodding. It has been felt that this adds to the total length of the procedure, that the general condition of the patient is not ideal and that usually the preoperative evaluation for the size of the nail, etc., has been inadequate. These factors probably add to the morbidity of the primary internal fixation of open fractures.

In a multiple injured patient, it is recommended waiting seven to 14 days before doing any elective major surgical procedure, such as intramedullary nailing, until the local effect of trauma has subsided and the condition of the patient is stable. The last two years we have not had a single infection following nailing at Hennepin County General Hospital or any infection during the last eight years at Methodist Hospital.

The disastrous results from an infection following nailing can be avoided by early diagnosis and immediate incision and drainage, adequate debridement and irrigation, irrigation, instillation of suction-irrigation set-up and administration of appropriate antibiotics intravenously in large doses. The nail should not be removed until the fracture is stable if not healed completely.

Open Reduction and Internal Fixation

The indication for open reduction and internal fixation are: (1) femoral shaft fractures through the isthmus, (2) any fracture of the femoral shaft which will lead to rigid fixation by intramedullary nailing with or without additional plate fixation, (3) any femoral shaft fracture with associated neurovascular complications, and (4) as prophylaxis for impending pathologic fractures.

If certain conditions are satisfied, the disadvantages to open reduction and internal fixation will be reduced greatly. These conditions are: (1) that the patient be in good condition for a surgical procedure, i.e., with adequate hemoglobin and no infections such as pneumonia or draining wounds; (2) that there exist an ideal and complete operating set-up including the preoperative measurements of the normal femur for length and canal size. (Even though this has been measured, there should be an assortment of rods and plates present); (3) that adequate surgical assistance be available—

the more experienced the assistant, the easier the operation; and, lastly as well as most importantly, (4) that the surgeon be experienced. More experienced surgeons take less time and have fewer complications.

Conclusions

From this study it has been shown that internal fixation presents great advantages over traction methods with regard to the period of recumbency, the duration of hospitalization, the rate of non-union and the quality of bone healing. The advantages of internal fixation offset the disadvantages if the cases are selected properly. If the requirements for intramedullary nailing cannot be met as outlined it should be recommended that the fracture be treated with traction.

Previous reports in the literature have decried open reduction as too risky for the benefits received. Recent advances in surgical technique, antibiotics, and good judgment are significant enough to warrant further contemplation. Since 1964 in this series there have been no infections following delayed internal fixation of open fractures. This stresses again the importance of waiting seven to 10 days for the wounds of open fractures to heal prior to internal fixation. If infection does ensue, early recognition, prompt installation of suction-irrigation and appropriate antibiotics will control the problem without removing the intramedullary nail.

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15-22. May be secured from the author or the reprint.

School of Salernum I

Complexions cannot vertue breed or vice,
Yet may they unto both give inclination,
The *Sanguine* game-some is, and nothing nice.
Loves Wine, and Women, and all recreation,
Likes pleasant tales, and news, playes, cards & dice,
Fit for all company, and every fashion:
Though bold, not apt to take offence, not irefull.
But bountifull, and kinde, and looking cheerefull:
Inclining to be fat, and prone to laughter,
Loves mirth, & Musick, cares not what comes after.

Editor's Note: For sheer camaraderie the School's sanguine *type would be one's choice of companion for a night on the town. He is an undiluted extrovert and hedonist: an engagingly irresponsible hail-fellow-well-met with no inhibitions. The artist's conception of the sanguine man shows him embracing a love partner.*

Radiologic Evaluation of the Lung Transplant

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SERIAL ROENTGENOGRAMS of the chest are indispensable in the follow-up of a lung transplant. In addition, angiography, bronchography, and radioisotope studies are useful in evaluating the anatomic and functional status of the graft. The present review deals with the application of these radiologic methods in various aspects of lung transplantation.

Autotransplantation (Reimplantation)

The immediate postoperative roentgenogram usually shows expansion of the autograft with a varying degree of radiopacity which, in the absence of complications, goes on to complete clearing. This may take three weeks in the dog,[15] and four to six weeks in the baboon.[17] The transient radiopacity is generally thought to represent edema or congestion.

Pneumothorax is a frequent complication,[17] and may be either ipsilateral, contralateral, or bilateral. Leakage of air along the suture tracts of the bronchial anastomosis usually accounts for the ipsilateral pneumothorax, while a tear of the mediastinal pleura is the likely cause of collapse of the opposite lung.

Atelectasis of a lobe or the entire autograft may occur as a result of bronchial plugging by secretion, or bronchostenosis,[17] which is caused by local ischemia of the bronchus distal to the anastomosis. It is believed that, after the lung is completely extirpated and then reimplanted, there is a collateral circulation between the pulmonary artery and the severed bronchial artery, bringing blood to the bronchial stump up to the line of anastomosis in a retrograde manner. Subsequently antegrade bronchial arterial blood flow is spontaneously restored, possibly within four weeks,[14] and may be demonstrated by bronchial arteriography.[1,14] If the collateral circulation is inadequate, ischemia of the bronchial stump will lead either to early necrosis or to stenosis at a later date. Morales[11] had found that a special technic preserving the bronchial artery during harvesting effectively prevents the bronchial complications.

Bronchostenosis with or without distal bronchiectasis is readily disclosed by bronchography.[6,7,17] In an uncomplicated case, the bronchographic appearance of the autograft is normal in the primate,[17] but may show poor periph-



Fig. 1—Left lung allograft in a baboon. Seventh postoperative day. The graft is completely radiopaque. (Reproduced with permission of Radiology 94:121-125, 1970).

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eral filling in the dog.[6] Bronchial dynamics of the reimplanted canine lung was studied by Blank et al.[1] using cinebronchography. They noticed bronchial contractions following intravenous injection of Methacholine chloride, and concluded that the myoelastic bronchial network was viable despite denervation of the bronchial tree.

Pulmonary angiography has been used to evaluate the site of pulmonary artery anastomosis. There may be diminished peripheral filling[15] of the arterial tree. Thrombosis of the pulmonary veins, a relatively common complication in the dog, causes obstruction or delayed filling and emptying of these veins on angiography.[16]

Lung scanning with I-131 tagged macroaggregated human serum albumin (Figure 2) is a very satisfactory way of assessing the blood flow of the graft.[19] Methods that use xenon-133 for determining the regional pulmonary ventilation and perfusion in the experimental animal have been described[12,18] and may be performed periodically for serial assessments of graft function. The functional recovery of the autograft as evaluated by conventional methods is uniformly better in the primate than in the dog.[7,9]

The lymphatic drainage of the reimplanted canine lung was studied by Eraslan and associates[5] by injecting Direct Sky Blue dye into the graft. They observed blue staining of restituted lymphatic channels across the bronchial anastomosis toward the end of the second week, and reaching the regional lymph nodes within three weeks. This restitution of the lymphatic drainage coincides with the radiographic resolution of the pulmonary edema. Pratt et al.[13] did a similar investigation employing colloid gold-198 as well as the dye. They noted that the lymphatic drainage was never completely interrupted, as radioactivity of low levels was demonstrated in the tissues and regional lymph nodes proximal to the bronchial anastomosis immediately after the reimplantation. This is understandable, because lymphatic vessels, unlike blood vessels, remain open after transection. Lymphatic flow thus persists, albeit at a much reduced level, and returns to normal after complete regeneration of the channels, thereby relieving the graft of its edema.

The effect of transplantation upon the bronchial cilia is a relatively unexplored area.[16] Among the existing methods of measuring ciliary activity, those employing radioactive particles[21] appear to be most suitable for in-vivo studies.

Autotransplantation of the human lung has been performed for the treatment of intractable bronchial asthma, because total pulmonary denervation is achieved after the extirpation of the lung prior to reimplantation. Meshalkin et al.[10] reported eight such operations on seven patients, one of whom received bilateral autografts in successive stages. Two patients died of pulmonary artery-bronchial fistula postoperatively, while all others experienced marked improvement. Unfortunately the roentgenograms of these patients were not shown in the published report.

Homotransplantation

With homotransplantation the phenomenon of rejection comes into play. Even between monozygotic identical twin calves the pulmo-



Fig. 2—Same baboon. Eighth postoperative day. Lung scan reveals complete absence of perfusion in the allograft. Decreased perfusion is noted in midfield of right lung, probably secondary to pneumonia. (Reproduced with permission of Radiology 94:121-125, 1970).

nary homografts were rejected within seven to eight weeks, by which time they appeared opacified on the roentgenogram.[2]

In a recent experiment,[19] 12 pairs of baboons, matched by major A, B, and O blood types, were subjected to cross allotransplantation of the left lung. Despite postoperative use of various immunosuppressive agents all animals died with evidence of graft rejection within three to 37 days. The early histological picture was one of edema and capillary engorgement, followed by progressive perivascular lymphocytic infiltration in some animals. With longer survival one noted increasing organization of edema fluid, and parenchymal consolidation. The septal capillaries became bloodless and obliterated by fibrous proliferation. Total rejection was associated with massive infarction of the graft. The roentgenograms revealed at first haziness of the lung field, then central cloudiness that spread toward the periphery until finally the entire graft was densely opaque (Figure 1). On lung scanning, perfusion of the graft was preserved if the capillary bed was not yet seriously compromised, but absent (Figure 2) if the bed was obliterated or effaced. In the latter event, the pulmonary arteriogram showed absence of contrast medium filling beyond the central portion of the arterial tree (Figure 3).

Buecherl[3] described progressive resorption of the canine allograft in several long-term survivors until the hemithorax was filled by the overexpanded contralateral lung, giving rise to a confusing roentgen appearance.

The first human lung transplantation was performed by Hardy[9] in 1963. By January 1970, an additional 22 cases had been done by 20 surgeons.[22] Subsequently Haglin operated on the 24th patient (Figure 4), the second lung transplantation case done at Hennepin County General Hospital. The indications for transplantation were pulmonary hypertension in two cases, and obstructive or restrictive respiratory insufficiency in 22 cases. The transplant consisted of either a lobe, a single lung, both lungs, or both lungs with the heart.

Out of these 24 patients, only one survived longer than 30 days,[4] and finally died with a rejected graft 10 months after the operation. The major postoperative problems were progressive respiratory insufficiency, despite the lung trans-



Fig. 3.—Same baboon. Eighth postoperative day. Pulmonary arteriogram disclosed absence of contrast medium beyond the proximal portions of the lobar arteries. The site of anastomosis (arrow) is patent. (Reproduced with permission of Radiology 94:121-125, 1970). Death occurred on the following day. At necropsy there was massive necrosis of the allograft with effacement of pulmonary architecture, including the capillaries.



Fig. 4—Forty-nine-year-old man who received bilateral lung transplants because of severe obstructive emphysema. Roentgenogram on the 11th postoperative day shows bilateral extensive infiltrative process and a left pneumothorax with chest tube. Death occurred on same day. At necropsy both lungs showed widespread edema with little evidence of rejection.

plantation, and massive pneumonia.[22] In patients who survived long enough for rejection to become a problem, the differential diagnosis between rejection and infection was difficult.[4,19] The radiographic finding of infiltration is entirely non-specific and may represent not only rejection or pneumonia, but other consolidating processes as well.

In Haglin's recent case, for example, the patient received bilateral lung transplants. Postoperatively antilymphocyte globulin, azathioprine, and corticosteroid were used for immunosuppression. Serial roentgenograms disclosed extensive infiltration in both grafts, worsening before death on the 11th day (Figure 4). At necropsy, both lungs were uniformly heavy and consolidated by widespread intra-alveolar edema in varying stages of organization. Perivascular and peribronchial lymphocytic infiltrations typical of immunologic rejection were notably inconspicuous and entirely absent in most areas. Patchy foci of a necrotizing bronchitis and pneumonitis were present, and these areas contained both mixed bacteria and candida spores. An acute lymphangitis and endovasculitis involving some pulmonary vessels were also evident. A detailed report of the case will be published elsewhere.[8]

It is possible that periodic measurements of regional function of the allograft may accurately predict an impending rejection.[20] The xenon-133 methods[12,18] should be useful in this respect and, in the human, carry less risk than bronchospirometry. Further evaluation of this method in both animal and human allografts is warranted.

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Editorials

Vacuum Curettage of the Uterus*

VACUUM CURETTAGE of the uterine cavity has been a widely employed method for terminating early pregnancies in Asia and Europe for the last decade. First described in China in 1958, the technique rapidly spread throughout the countries of Asia and Europe that had liberal laws permitting induced abortions. Also called "uterine aspiration," "suction evacuation," or "suction curettage," this technique has been used to perform many thousands of induced abortions each year in these countries.

In the United States, the acceptance of vacuum curettage as a method for evacuating the uterus has been slow. Until recently, strict laws have limited the number of induced abortions. Now, with more liberal abortion laws, many more medical institutions are employing vacuum curettage not only for therapeutic abortions but also for evacuation of incomplete spontaneous abortions or hydatidiform moles.

The basic technique for vacuum curettage is to aspirate the conceptus from the uterus using a tube with a flexible connection to a suction pump. The operation may be performed with general, local, or even no anesthesia depending on the condition of the patient and her cervix. When the cervix is dilated, aspiration often requires only two to three minutes. The negative pressure employed should not exceed one atmosphere (1 kg/sq cm or 30 inches of mercury). The usual range of negative pressure used is from 0.4 to 1.0 atmosphere.

Vacuum curettage has several advantages over mechanical curettage of the uterine cavity. With vacuum curettage, the operating time is shorter, the chances of uterine perforation or spread of infection are less, and the amount of blood lost is usually less. With suction curettage, it is possible to aspirate the uterine contents through only a slightly dilated cervical os with decreased trauma to the myometrium. With mechanical curettage, more profound levels of anesthesia are required.

The disadvantages of vacuum curettage include the fact that sometimes adherent trophoblastic tissue is not evacuated; the apparatus, which is somewhat costly, occasionally does not function properly and is time-consuming to prepare and sterilize; and immediate inspection of the evacuated tissue by the obstetrician is more difficult.

For clinical practice, vacuum curettage offers advantages over mechanical curettage for the evacuation of induced abortions up to 10 or 12 weeks of gestation, for evacuation of infected abortions, and for evacuation of hydatidiform moles of all sizes. Suction aspiration also has been useful for the early treatment of incomplete abortions. However, this method has been found to be less successful for the late treatment of incomplete abortions when the cervix has contracted and when trophoblastic tissue is more adherent. Most obstetricians consider vacuum curettage an unsuitable method for evacuating missed abortions. This type of curettage is not indicated as a diagnostic gynecologic procedure.

Leonard A. Aaro, M.D.†
Rochester, Minnesota

*Hill, David: Management of Incomplete Abortion with Vacuum Curettage. Minnesota Med 54:225, 1971.

†Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Noludar® 300
(methyprylon)

one capsule
for the rest
of the night



Before prescribing, please consult complete product information, a summary of which follows:

INDICATION: Relief of insomnia of varied etiology.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug.

WARNINGS: Caution patients about combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle shortly after ingesting the drug.

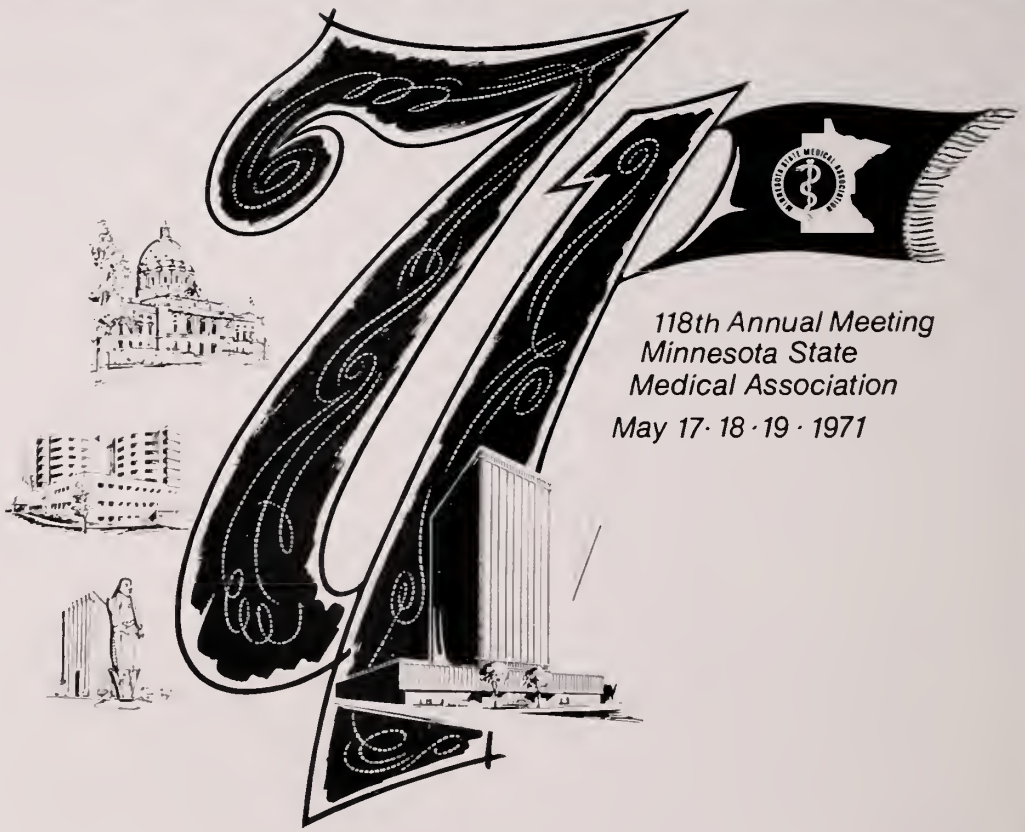
Physical and Psychological Dependence: Physical and psychological dependence rarely reported. If withdrawal symptoms do occur they may resemble those associated with withdrawal of barbiturates and should be treated in the same fashion. Use caution in administering to individuals known to be addiction-prone or those whose history suggests they may increase the dosage on their own initiative. Repeat prescriptions should be under adequate medical supervision.

Usage in Pregnancy: Weigh potential benefits in pregnancy, during lactation, or in women of childbearing age against possible hazards to mother and child.

PRECAUTIONS: If sleeplessness is pain-related, an analgesic should also be prescribed. Perform periodic blood counts if used repeatedly or over prolonged periods. Total daily intake should not exceed 400 mg, as greater amounts do not significantly increase hypnotic benefits.

ADVERSE REACTIONS: At recommended dosages, there have been rare occurrences of morning drowsiness, dizziness, mild to moderate gastric upset (including diarrhea, esophagitis, nausea and vomiting), headache, paradoxical excitation and skin rash. There have been a very few isolated reports of neutropenia and thrombocytopenia; however, the evidence does not establish that these reactions are related to the drug.

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The Odontoid Fracture*

The capriciousness of the odontoid fracture is discussed knowingly elsewhere in this issue from a broad clinical background. Its frequent association with high-speed, decelerating accidents causing closed and open head injuries, facial lacerations, fractures of long bones, and visceral injuries can easily lead to diagnostic omission as the physician takes inventory of the multiplicity of injuries.

Most physicians and emergency room personnel currently understand the necessity of obtaining roentgenograms of the cervical spine of unconscious patients and patients with injuries to the head and neck. It probably should be emphasized again, however, that open-mouth odontoid views or planograms of the odontoid region are necessary as screening procedures if there is the slightest suspicion of injury at the odontoid level, just as it is frequently necessary to obtain special views of the lower cervical spine in the heavily muscled or short-necked male.

Flexion-extension views of the neck may also be necessary if atlantoaxial forward subluxation cannot be excluded. An interval of more than 3 mm between the posterior margin of the anterior arch of the atlas and the anterior surface of the odontoid is considered the maximal excursion in adults, with 5 mm being considered maximal in younger children. The possibility of atlantoaxial subluxation with tetraparesis should be considered in patients with long-standing rheumatoid arthritis, especially in those who have been on heavy steroid dosages, because this is a frequent complication of the disease.

Reduction and stabilization can usually be obtained with Crutchfield tongs even in the patient with multiple injuries. The advent of the halo device for firm cranial stabilization to a body cast and good cervicothoracic braces lends greater versatility to the management of these injuries.

The malunited or anteriorly subluxed ununited odontoid with pseudarthrosis together with the inherent danger of cord compression gives rise to pain in the neck and increased pain in the occipital region as well as muscle fatigue caused by the difficulty in balancing the head over the spinal column in its forward subluxed position. Though atlantoaxial arthrodesis is an acceptable treatment for this condition, the risk of surgical treatment and the morbidity from the operation are far less desirable than early diagnosis and spontaneous union.

Ronald L. Linscheid, M.D.
Rochester, Minnesota

*See page 241.

Cover Photo

Louis A. Buie, Sr., M.D.

South Carolina, Remembered

Sir Winston Churchill took up painting at the age 40. Dr. Louis Buie of the Emeritus Staff of the Mayo Foundation waited until he was well past 70, and started then only because, during an illness, "my wife encouraged me to try." So energetically did he follow her advice that the Buie recreation room turned studio now hardly holds all his canvases. "I could always sketch."

Dr Buie is a world-famous proctologist and one of the first in his specialty for whom he has high regard. With oils he paints, "things I remember," and his memory is long, extending back to scenes of his South Carolina youth.

Dr. Buie is a world famous proctologist and one of the first in his specialty working with the Mayo Brothers in Rochester.

Hepatitis Grave

ACUTE HEPATIC FAILURE due to viral hepatitis, drug reactions or poisonings is an uncommon event, but it carries a mortality rate of approximately 80 percent. Because it is rare, physicians depend upon collective experiences for much of their knowledge of this grave problem, and it is gratifying to study the report of 87 cases reported in this issue by Doctors Rueff, Menache, Sicot and Benhamou.* Their report can be compared with that of the Fulminant Hepatic Failure Surveillance Study in this country, which thus far has pooled the experiences from 98 centers of 318 instances of acute hepatic failure.

Viewing the syndrome as an acute functional hepatectomy, one realizes the difference between hepatic coma occurring in chronic or even subacute hepatic disease, and the liver failure of acute fulminant hepatitis. Coma arising in the course of chronic liver disease usually does not imply such a total loss of hepatic function as does fulminant hepatitis, and its management depends upon efforts to arrest a continuing pathological process and to reverse or eliminate situations that precipitate coma in an otherwise compensated, albeit chronically damaged, liver.

In our opinion, the diagnosis of fulminant hepatic failure or *hepatitis grave* should imply the concept of a sudden functional hepatectomy wherein liver failure follows closely upon massive hepatocellular necrosis. Usually one is not dealing with this entity if the patient develops coma later than six to eight weeks after the onset of viral hepatitis, or later than two weeks following acute poisonings or drug reactions.

The survival of a patient with fulminant hepatic failure depends upon the ability of his liver to regenerate sufficient hepatocytes to support life and upon the ability of the clinician to maintain him until this occurs.

Knowledge of the malfunction of the central nervous system and the pathophysiology of hemostasis, ventilation and cardiovascular function is most helpful to the physician attempting to support the patient who lacks liver function.

The occurrence of consumption coagulopathy in acute hepatic failure has not been emphasized in this country. The addition of the hematologist to the team endeavoring to save these patients may allow temporary control of this pathophysiologic complication. Cardiovascular complications of fulminant hepatitis have also received little attention in the United States. The author's description of the hyperkinetic state of the cardiovascular system which can lead to cardiovascular collapse should alert our clinicians to this potential problem. Rueff et al. do not emphasize renal failure, respiratory failure per se or massive hemorrhage as major problems in this syndrome; but in this country these complications have been implicated in the majority of deaths due to acute hepatic failure.

Life support by means of exchange transfusions or cross circulation has theoretical appeal for the treatment of fulminant hepatitis, but neither has yet clearly improved the overall prognosis. Massive steroid therapy is often tried, but this treatment also lacks proven benefit.

In the United States, prognosis has been related to age. Patients under 15 years had about a 65% mortality, those between 15 and 44 years, a 78% mortality, while mortality in patients over 45 years was 95%. Also, in the United States experience, patients with hepatic failure associated with Halothane anesthesia constituted a prominent subgroup (20% among all cases) with a high mortality (85-90%).

The continued collection of experience from cases of acute hepatic failure will improve our diagnostic and therapeutic skills. With broader knowledge of the pathophysiology of *hepatitis grave,* hopefully we will develop more specific life support systems and reduce its high mortality.

Don P. Jones, M.D.†
Joseph B. Kirsner, M.D.†
Chicago, Illinois

*Rueff, B., Menache, Doris, Sicot, C. and Benhamou, J.-P.: Acute Comatose Hepatitis—Symptomatology and Natural Course. Minnesota Med 54:91, 1971.

†Department of Medicine, University of Chicago.

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Contraindications: Known sensitivity to sulfonomides.
Precautions/Adverse Reactions: The usual precautions for topical and systemic sulfonomides should be observed because of the possibility of absorption. Burning, increased local discomfort, skin rosh, urticoria or other manifestations of sulfanamide toxicity ore reasons to discontinue treotment.
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Brief Summary. Blurring of vision, dry mouth, diff cult urination, and flushing or dryness of the skin ma occur on higher dosage levels, rarely on usual dosag Administer with caution to patients with incipier glaucoma or urinary bladder neck obstruction. Contra indicated in acute glaucoma, advanced renal or hepati disease or a hypersensitivity to any of the ingredient

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The Editor's Soliloquy

The Doctor's Wife

THE DOCTOR'S WIFE is the most wonderful, loving wife in the world. She thinks her husband is great, brilliant, and she knows he is serving a noble cause for humanity. She defends his opinion, over the objections of everyone; but that's not the issue at the moment.

The doctor's wife should have studied medicine and then specialized in the etiology of disease, because she always wants to know specifically why *her* kids get the measles and not the kids across the street; or she wants to know why the Lord had to let the doctor sprain his ankle when it would have been much more practical if He had let one of those unemployed gentlemen sitting on the curb get the sprain. Those fellows have nothing to do anyway; they are jobless and may even be unemployable besides; they are contributing nothing to society. She thinks, on the other hand, that her doctor husband is supposed to be up and doing, rendering service to humanity instead of loafing around the house with a sprained ankle. She gives no consideration whatsoever either to his clumsiness or to the laws of nature.

When she gets a sore spot she can't understand why her doctor husband can't see or feel it. When he suggests that her sore spot is only a muscle, her fears are somewhat alleviated. She is glad it wasn't a bone or a nerve or a ligament or a blood vessel or something vital that might induce cancer. To her, muscles seem to be expendable and it's all right if it's nothing more than a muscle. The doctor doesn't dare to tell her that a highly malignant rhabdomyosarcoma originates in the muscle, because she would never again allow him off so lightly, as hitherto.

She consults her doctor-husband on medical problems relating to the children but she always ends up using Vick's Vapo-Rub and she can't understand why doctors and Dahl's Drugs won't recommend it to their customers, since she has found it to be the most universal cure-all. To her spouse it is reminiscent of the smell at the Union City Mission or the County Jail when he was an intern and had to make an emergency call.

The doctor's wife categorizes animals, plants and people into one homogeneous group; she doesn't like grackles, creeping Charlie, and some people because they're so hard to get rid of, but she loves old married couples, geese and jack-in-the-pulpits because they are so loyal to their mates. She smiles upon mother birds, mother cows, mother jackals and all other mothers that attend their young, but she frowns on mother turtles that lay their eggs and then let the babies hatch and survive as best they can on their own.

Good politician that she is and knowledgable about all the laws that clutter up the statute books, she always has another ordinance in mind, e.g., one against the people who honk their horns at women drivers who might be doing nothing more than applying lipstick when a red traffic sign turns green ("what's their hurry, anyway?") She has even hinted that there should be a law against spinach, motorcycles, rattlesnakes, parties at the Country Club and beautiful secretaries.

The doctor's wife is a wonderful woman. She has to be if she is married to a doctor!

—Carl O. Rice, M.D.
Editor-in-Chief

OLD DOC HESS SAYS: An untruth, though innocently conceived, may linger long.—C.O.R.

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Pro-Banthine 15 mg. propantheline bromide with Phenobarbital 15 mg. warning: may be habit forming

Pro-Banthine P.A. 30 mg. propantheline bromide in time-release form

Pro-Banthine 7½ mg. propantheline bromide Half Strength



Pro·Banthine®
(propantheline bromide)

Indications: Peptic ulcer, gastroenteritis, pylorospasm, biliary dyskinesia, functional hypermotility and irritable colon.

Contraindications: Glaucoma, severe cardiac disease.

Precautions: Since varying degrees of urinary hesitancy may occur in elderly men with prostatic hypertrophy, this should be watched for in such patients until they have gained some experience with the drug. Although never reported, theoretically a curare-like action may occur with possible loss of voluntary muscle control. Such patients should receive prompt and continuing artificial respiration until the drug effect has been exhausted.

Side Effects: The more common side effects, in order of incidence, are xerostomia, mydriasis, hesitancy of urination and gastric fullness.

Dosage: The maximal tolerated dosage is usually the most effective. For most adult patients this will be four to six 15-mg. tablets daily in divided doses. In severe conditions as many as two tablets four to six times daily may be required. Pro-Banthine is supplied as tablets of 15 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg. The parenteral dose should be adjusted to the patient's requirement and may be up to 30 mg. or more every six hours, intramuscularly or intravenously.

Pro-Banthine® 15 mg.
(propantheline bromide)
with
Dartal® 5 mg.
(thiopropazate dihydrochloride)

Indications: Peptic ulcer, spastic constipation, nonspecific gastritis, functional gastrointestinal disorders, pylorospasm, hyperhidrosis, irritable bowel syndrome, mucous or ulcerative colitis, functional diarrhea.

Contraindications: Glaucoma, severe cardiac disease.

Warnings: Pro-Banthine with Dartal should not be administered to patients who are under the influence of barbiturates, alcohol or narcotics. The drug should be administered cautiously to epileptic patients or those in depressed states, patients with liver disease and to pregnant women. Hypersensitivity to Dartal may occur rarely in patients with known sensitivity to similar drugs.

Side Effects: Dryness of the mouth, mydriasis, hesitancy of urination; less commonly extrapyramidal (restlessness, dystonia and signs of pseudoparkinsonism such as muscular rigidity, fixed facies, tremor, ataxia, festinant gait and drooling), parasympatholytic (blurred vision, xerostomia, hypotension, nasal congestion and constipation) and curare-like (loss of control of voluntary muscles, particularly the muscles of respiration) reactions. Rarely, leukopenia or allergic purpura. A generalized erythematous skin reaction may occur. Side effects characteristic of phenothiazines such as grand mal convulsions, altered cerebrospinal proteins, cerebral edema, potentiation of the effects of atropine, heat or phosphorus insecticides, autonomic reactions, endocrine disturbances, reversed epinephrine effect, hyperpyrexia or pigmentary retinopathy may theoretically occur but have not been reported with Dartal. Severe hypotension following recommended doses occurs more commonly in patients who are also afflicted by other medical disorders such as mitral insufficiency or pheochromocytoma, and particular attention should be paid to such a possibility although this has not been observed with Dartal.

Adult Dosage: One tablet three times a day.

Pro-Banthine® 15 mg.
(propantheline bromide)
with
Phenobarbital 15 mg.

Warning: May be habit-forming.

For *Indications, Contraindications, Precautions, Side Effects* and *Dosage* see Pro-Banthine. In addition, phenobarbital should be administered with caution to patients with liver disease, mental disturbances or a significant degree of hypoxia.

Pro-Banthine P.A.®
prolonged acting brand of propantheline bromide

For *Indications, Contraindications, Precautions* and *Side Effects* see Pro-Banthine.

Dosage Form: Capsule-shaped, compression-coated, peach tablets of 30 mg. for oral use.

Dosage: The recommended initial dosage is one tablet in the morning and one at night.

084

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You May Be Right

A Point of Honor

A frequent criticism of modern medicine is that the doctor-patient relationship is not as good as it used to be. Our ability to save more lives and to treat disease better have been compromised, it is said, by lack of humanity, sympathy and identification with those in need. The truth of these charges could be argued; however, there is one small area where my experience has indicated we could do better.

Autopsy rate has been used by accreditation committees and others as an index of a hospital's commitment to excellence. Many institutions stimulate their house staff to get a "post." Permission is frequently obtained by telling the family that information obtained by such an examination not only would be used by the medical staff to help similar patients in the future, but would be made available to the relatives in language that they could understand. This commitment, given at a time of great emotional distress for the family, is too often dishonored. There are many reasons for this.

Such problems are almost unknown in smaller communities with a simpler pattern of medical practice but are common in larger clinics and hospitals. Probably the only way to avoid public resentment of the medical profession for such breach of promise is to have the chief of the clinical department hold himself responsible for seeing that, whenever a death certificate is signed on his service, a letter of condolence containing preliminary results of the autopsy examination be sent to the deceased's family.

Raymond C. Read, M.D.*
Little Rock, Arkansas

*Chief, Surgical Service, Veterans Administration Hospital, Little Rock, Arkansas and Professor of Surgery, University of Arkansas Medical School.

Enema Can Be a Dangerous Act*

Approximately one year ago, while in the Air Force, I took care of a 24-year-old-Caucasian female gravida 1, para 0. She came to the labor and delivery area of USAF Hospital, Keesler, at term in early labor. She had not had a bowel movement for the previous four days. As was routine at that time, she received a soapsuds enema on admission. While straining unsuccessfully on the toilet, she fainted. She was immediately put to bed and found to be cyanotic and shocky. Her blood pressure was zero, and there were no fetal heart tones. Hematocrit was 72 percent. Intravenous-Ringer's lactate infusion was started, and after a large amount of intravenous infusion and vasopressor medication the patient recovered from her cardiovascular collapse. A few hours later she delivered a stillborn infant. Approximately 12 hours after delivery, the patient had a large, hard bowel movement which was followed with four bedpans full of clear and blood-tinged fluid. Subsequently she made an uneventful recovery.

In reconstructing the clinical situation, the patient was thought to have had a contact allergic reaction to the soap which then led to massive transudation of fluid, sudden hypotension and cardiovascular collapse, resulting in death of the fetus from hypoxia.

Fortunately prompt treatment prevented maternal death. I am in complete agreement with abandoning soapsuds enemas altogether, as is the staff at Keesler Air Force Hospital.

Stephen L. Larson, M.D.
Minneapolis, Minnesota

*Editorial by W. C. Bernstein, Minnesota Med 53:1181, 1970.

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Contraindications: Concurrently with MAO inhibitors, in patients hypersensitive to drug; in emotionally unstable patients susceptible to drug abuse.

Warning: Although generally safer than the amphetamines, use with great caution in patients with severe hypertension or severe cardiovascular disease. Do not use during first trimester of pregnancy unless potential benefits outweigh potential risks.

Adverse Reactions: Rarely severe enough to require discontinuation of therapy, unpleasant symptoms with diethylpropion hydrochloride have been reported to occur in relatively low incidence. As is characteristic of sympathomimetic agents, it may occasionally cause CNS effects such as insomnia, nervousness, dizziness, anxiety, and jitteriness. In contrast, CNS depression has been reported. In a few epileptics an increase in convulsive episodes has been reported. Sympathomimetic cardiovascular effects reported include ones such as tachycardia, precordial pain, arrhythmia, palpitation, and increased blood pressure. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride; this was an isolated experience, which has not been reported by others. Allergic phenomena reported include such conditions as rash, urticaria, ecchymosis, and erythema. Gastrointestinal effects such as diarrhea, constipation, nausea, vomiting, and abdominal discomfort have been reported. Specific reports on the hematopoietic system include two each of bone marrow depression, agranulocytosis, and leukopenia. A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dry mouth, headache, dyspnea, menstrual upset, hair loss, muscle pain, decreased libido, dysuria, and polyuria.

Convenience of two dosage forms: TEPANIL Ten-tab tablets: One 75 mg. tablet daily, swallowed whole, in midmorning (10 a.m.); TEPANIL: One 25 mg. tablet three times daily, one hour before meals. If desired, an additional tablet may be given in midevening to overcome night hunger. Use in children under 12 years of age is not recommended.

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Prescribing Information—Composition: Each white, beveled, compressed tablet contains: Quinine sulfate, 260 mg., Aminophylline, 195 mg. **Indications:** For the prevention and treatment of nocturnal and recumbency leg muscle cramps, including those associated with arthritis, diabetes, varicose veins, thrombophlebitis, arteriosclerosis and static foot deformities. **Contraindications:** QUINAMM is contraindicated in pregnancy because of its quinine content. **Precautions/Adverse Reactions:** Aminophylline may produce intestinal cramps in some instances, and quinine may produce symptoms of cinchonism, such as tinnitus, dizziness, and gastrointestinal disturbance. Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. **Dosage:** One tablet upon retiring. Where necessary, dosage may be increased to one tablet following the evening meal and one tablet upon retiring. **Supplied:** Bottles of 100 and 500 tablets.

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DOSAGE: One tablet or capsule every 6 hours will sustain mild sedation.

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Minnesota State Medical Association 118th Annual Meeting

Saint Paul, Minnesota

May 17, 18, 19, 1971

Suddenly in Saint Paul . . .

The sound of the speaker's gavel will call to order the House of Delegates on Sunday, May 16, at 2:00 P.M. in the Continental Room, Hotel St. Paul.

It will also mark the official opening of the 118th Annual Meeting of the Minnesota State Medical Association May 17, 18 and 19, 1971.

For these three important days in May, St. Paul will be the host city for the upper midwest's great medical meeting.

Following the opening session of the House, reference committees will meet Sunday at 7:30 P.M. to consider the reports of officers, councilors, committees and other special reports. Reference Committees will also consider resolutions which have been submitted by the Council, county medical societies, medical specialty groups and members of the House of Delegates. Sponsors of all resolutions or their representatives are advised to be present when their resolutions are considered by the reference committees and the House. Sponsors will be advised as to the specific committee to which their resolution is referred.

Doctor Raymond J. Jackman, President of the Minnesota State Medical Association, will present his report at the opening session. Reports of other Association officers customarily presented at the opening session include those given by the chairman of the Council, and the chairman of the Finance Committee.

Delegates will also receive the reports of the Minnesota Board of Examiners in the Basic Sciences, the Minnesota State Board of Medical Examiners and the Minnesota Department of Health.

Other presentations scheduled for the opening session include the 1970 contribution from AMA-ERF to the University of Minnesota Medical School and the acceptance for the medical school. Presentation of Rural Family Practice Scholarships will be made during this session, also the MINNESOTA MEDICINE writing awards.

The report of the Woman's Auxiliary to the Minnesota State Medical Association will be presented by Mrs. Cyril Tifft, State President.

The House will reconvene Tuesday, May 18, at 2:00 P.M. to consider and act upon the reports of reference committees, transact new business and elect officers for the coming year.

The annual banquet, a traditional social highlight of the meeting, is scheduled for 7:00 P.M. in the Continental Room, Hotel St. Paul. Fifty Club members will be honored banquet guests. Banquet entertainment will be provided by the 3M Music Makers. The President's Reception, beginning at 6:00 P.M., will precede the banquet.

The opening scientific session is scheduled to begin Monday, May 17, at 9:00 A.M. at the St. Paul Hilton, and will feature a three part presentation on Acute Respiratory Failure. The second Monday morning session will be devoted to Antibiotics, also a three part presentation.

"Disease in Families: A Survey of the General Practice of Genetics" is the title of the opening Tuesday morning session. The Intensive Coronary Care Unit Committee of the Minnesota Heart Association will present the second session on Tuesday morning at 10:30

A.M. The title of this session is "Major Complications of Acute Cardiac Infarction."

The Wednesday morning sessions have been arranged by the Minnesota Chapter of the American College of Surgeons and will be devoted to a two part presentation on TRAUMA. The concluding portion of the American College of Surgeons session will feature a panel to which the audience may direct questions and discussion.

Two groups of the perennially popular workshops have been scheduled for Monday and Tuesday afternoons. Identical workshop sessions have been scheduled from 2:00 to 3:00 P.M. and 3:45 to 4:45 P.M. both days. The Monday schedule of workshops is as follows: "Consumptive Coagulopathy—Intravascular Coagulation and Fibrinolysis (ICF) Syndrome," "Diagnosis of Thyroid Disorders," "Oral Hypoglycemic Agents," "Gastrointestinal Bleeding," "The Dizzy Patient" and "Aneurysms." Three workshops have been arranged for Tuesday, and include the following: "L-Dopa," "Surgical Emergencies in the Newborn" and "Handling and Moving the Injured Patient."

Modern concepts of the treatment of chemical addiction—alcoholism and drug abuse—involve the mobilization and combined efforts of many segments of the professional community. Physicians and clergymen have been generally recognized as playing a key role in the rehabilitation of the chemical drug abuser. Among leaders in both professions there is also an increased awareness of the responsibility which is theirs to inform, to educate and to motivate action to implement resources to deal with this problem. Through the combined efforts of the Committee on Medicine and Religion and the Sub-Committee on Alcoholism and Drug Abuse a three and one-half hour forum on alcoholism and drug abuse has been scheduled for Tuesday afternoon at 1:30 P.M.

The program includes a panel of four out-of-state guest speakers of national renown. Invitations have been extended to members of the clergy to join physicians in this frank and educational program. Physicians are asked to write and encourage their personal clergymen to join them in attending this timely presentation.

The noon luncheon on Monday, May 17, will feature the presentation "Communication—Who Needs It?" by Doctor James F. Martin, Minneapolis, Consulting Psychologist. On Tuesday Mr. Gregg Orwoll, Attorney, Rochester, will be the luncheon speaker. His topic will be "Law and Medicine—Continuing Conflict."

A number of specialty groups have scheduled meetings in conjunction with the Annual Meeting. They include the following: The Minnesota Physiatric Society, Tuesday, May 18 (Dinner Meeting); The Minnesota Academy of Ophthalmology and Otolaryngology, Tuesday, May 18 (Dinner Dance); the Minnesota Chapter of the American Academy of Pediatrics, Tuesday, May 18 (Evening); and the Minnesota Chapter of the American College of Surgeons, Wednesday, May 19 (Noon) with a socio-economic and business session at 1:30.

Additional details of the Upper Midwest's Great Medical Meeting will appear in future issues of the NEWSPAGE, MINNESOTA MEDICINE and the official program which will be mailed to all members.

The new and exciting St. Paul Hilton Hotel will provide a unique setting for scientific sessions, workshops, committee breakfasts and scientific and technical exhibits. The "all under one roof" hotel-based setting promises to provide a new dimension for physicians attending the meeting.

The annual Physicians' Golf Tournament will get under way Sunday, May 16, at 10:00 A.M. at Dellwood Hills Country Club, White Bear Lake. Green fees are $6.00. Participants in the golf tournament, their wives and all physicians who attend the Annual Meeting are invited to attend a buffet dinner at 5:30 P.M. at the Dellwood Hills Country Club. Buffet tickets are $6.00 per person.

SCIENTIFIC PROGRAM

St. Paul Hilton Hotel

MONDAY, MAY 17

9:00 A.M. to 10:00 A.M. ACUTE RESPIRATORY FAILURE

1) "Causes and Recognition"
M. B. Divertie, M.D., Rochester

2) "Management of the Airway and Control of Secretions"
E. P. Didier, M.D., Rochester

3) "Use of Oxygen and Assisted Ventilation"
Hugh D. Westgate, M.D., Minneapolis

10:00 A.M.—
10:30 A.M. INTERMISSION
Visit Scientific and Technical Exhibits

10:30 A.M.—
12:00 Noon ANTIBIOTICS

1) "Antibiotic Combinations and Gram-Negative Infections"
Wallace E. Herrell, M.D., Editor, Clinical Medicine, Northfield, Illinois

2) "Antibiotic Treatment of Gram-Negative Bacteremias"
Paul E. Hermans, M.D., Rochester

3) "Shock Associated with Gram-Negative Bacteremias"
Wendell Hall, M.D., Minneapolis

12:15 P.M. LUNCHEON
Dr. James F. Martin, Consulting Psychologist, Minneapolis "COMMUNICATION—WHO NEEDS IT?"

WORKSHOPS

2:00 P.M.—
3:00 P.M. 1) "Consumptive Coagulopathy—Intravascular Coagulation and Fibrinolysis (ICF) Syndrome"
F. J. Kazmier, M.D. and Paul Didisheim, M.D., Rochester

2) "Diagnosis of Thyroid Disorders"
Horace K. Ivy, M.D., Rochester

3) "Oral Hypoglycemic Agents"
Frederick C. Goetz, M.D. Minneapolis

4) "Gastrointestinal Bleeding"
Philip W. Brown, Jr., M.D., Donald C. McIlrath, M.D., Rochester

5) "The Dizzy Patient"
Frank M. Howard, Jr., M.D., Lawrence W. DeSanto, M.D., Rochester

6) "Aortic Aneurysms"
Philip J. Osmundson, M.D., James R. Pluth, M.D., Rochester

REPEATED
3:45 P.M.—
4:45 P.M.

MONDAY EVENING — BANQUET

TUESDAY, MAY 18

9:00 A.M.—
10:00 A.M. "Disease in Families: A Survey of the General Practice of Genetics"
Hymie Gordon, M.D., Rochester

10:00 A.M.—
10:30 A.M. INTERMISSION
Visit Scientific and Technical Exhibits

10:30 A.M.—
12:00 Noon MAJOR COMPLICATIONS OF ACUTE CARDIAC INFARCTION
Presented by: Intensive Coronary Care Unit Committee of the Minnesota Heart Association.
Moderator: E. R. Giuliani, M.D., President-Elect, Minnesota Heart Association

10:30 A.M. "Heart Block"
Brian Campion, M.D., St. Paul

10:50 A.M. "Power Failure"
John Stokes, M.D., Rochester

11:10 A.M. "Rupture, VSD and Mitral Valve Dysfunction"
E. R. Giuliani, M.D., Rochester

11:30 A.M.—
12:00 Noon ROUND TABLE DISCUSSION

12:15 P.M. LUNCHEON
Gregg Orwoll, Attorney, Rochester
"LAW AND MEDICINE—CONTINUING CONFLICT"

1:30 P.M.—
5:00 P.M. ALCOHOLISM AND DRUG ABUSE FORUM
Moderator: Donald H. Petersen, M.D., Willmar
Participants: Rev. John E. Keller, Chicago
Rev. Philip Hansen, White Bear Lake
Richard O. Heilman, M.D., Minneapolis
Milton Kepler, Jr., M.D., Univ. of Nebraska, Lincoln
Graham B. Blaine, Jr., M.D., Harvard University, Cambridge, Massachusetts
Philip M. Margolis, M.D., Ann Arbor, Michigan

WORKSHOPS

2:00 P.M.—
3:00 P.M. 1) "L-Dopa"
Manfred D. Muenter, M.D., Rochester

2) "Surgical Emergencies in the Newborn"
Bernard J. Spencer, M.D., Minneapolis
Hugh B. Lynn, M.D., Rochester

3) "Handling and Moving the Injured Patient"
Phillip E. Richards, State Dept. of Health
S. R. Maxeiner, Jr., M.D., Minneapolis

REPEATED
3:45 P.M.—
4:45 P.M.

WEDNESDAY MORNING, May 19—Arranged by:

Minnesota Chapter of American College of Surgeons
Lyle J. Hay, M.D., President, Minnesota Chapter American College of Surgeons, Presiding

TRAUMA—PART I

9:00 A.M. "Facial Fractures and Injuries"
John N. Simons, M.D., Rochester

9:10 A.M. Discussion

9:20 A.M. "The Early Management of Burns"
James W. LaFave, M.D., St. Paul

9:30 A.M. Discussion

9:40 A.M. "Treatment of Fingertip Injuries"
James H. Dobyns, M.D., Rochester

9:50 A.M. Discussion

10:00 A.M. INTERMISSION

TRAUMA—PART II

S. R. Maxeiner, Jr., M.D., Minneapolis, Presiding

10:30 A.M. "Initial Treatment of the Patient with Multiple Injuries"
John F. Perry, Jr., M.D., St. Paul

10:45 A.M. "Trauma and the Lung"
Richard L. Simmons, M.D., Minneapolis

11:00 A.M. "Management and Prevention of Renal Failure in Trauma"
Fred L. Shapiro, M.D., Minneapolis

11:15 A.M.- **PANEL**—Questions and Discussion
12:00 Noon Albert Mowlem, M.D., Moderator, St. Paul
Panelists: John F. Perry, Jr., M.D.
Richard L. Simmons, M.D.
Fred L. Shapiro, M.D.

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Proloid® (thyroglobulin)

Description: Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, sodium levothyroxine (T_4) and sodium liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.

Chromatographic analysis to standardize the sodium levothyroxine and sodium liothyronine content of Proloid (thyroglobulin) is routinely employed.

The ratio of T_4 and T_3 in Proloid (thyroglobulin) is approximately 2.5 to 1.

Proloid (thyroglobulin) is stable when stored at usual room temperature.

Indications: Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.

Contraindication: Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.

Warnings: Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid, and dosage should be started at a very low level and increased gradually.

Precaution: As with all thyroid preparations this drug will alter results of thyroid function tests.

Adverse Reactions: Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration: Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, T_3 ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.

Instructions for Use: The following conversion table lists the approximate equivalents of other thyroid preparations to Proloid (thyroglobulin) when changing medication from desiccated thyroid, T_4 (sodium levothyroxine), T_3 (sodium liothyronine), or T_4/T_3 (liotrix).

Dose of Proloid (thyroglobulin)	Dose of desiccated thyroid	Dose of T_4 (sodium levothyroxine)	Dose of T_3 (sodium liothyronine)	Dose of liotrix (T_4/T_3)
1 grain	1 grain	0.1 mg	25 mcg	±1 (60 mcg/15 mcg)
2 grains	2 grains	0.2 mg	50 mcg	±2 (120 mcg/30 mcg)
3 grains	3 grains	0.3 mg	75 mcg	±3 (180 mcg/45 mcg)
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.

Overdosage Symptoms: Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

How Supplied: ¼ grain; ½ grain; scored 1 grain; 1½ grain; 3 grain; and scored 5 grain tablets, in bottles of 100 & 1000; and scored 2 grain tablets in bottles of 100.

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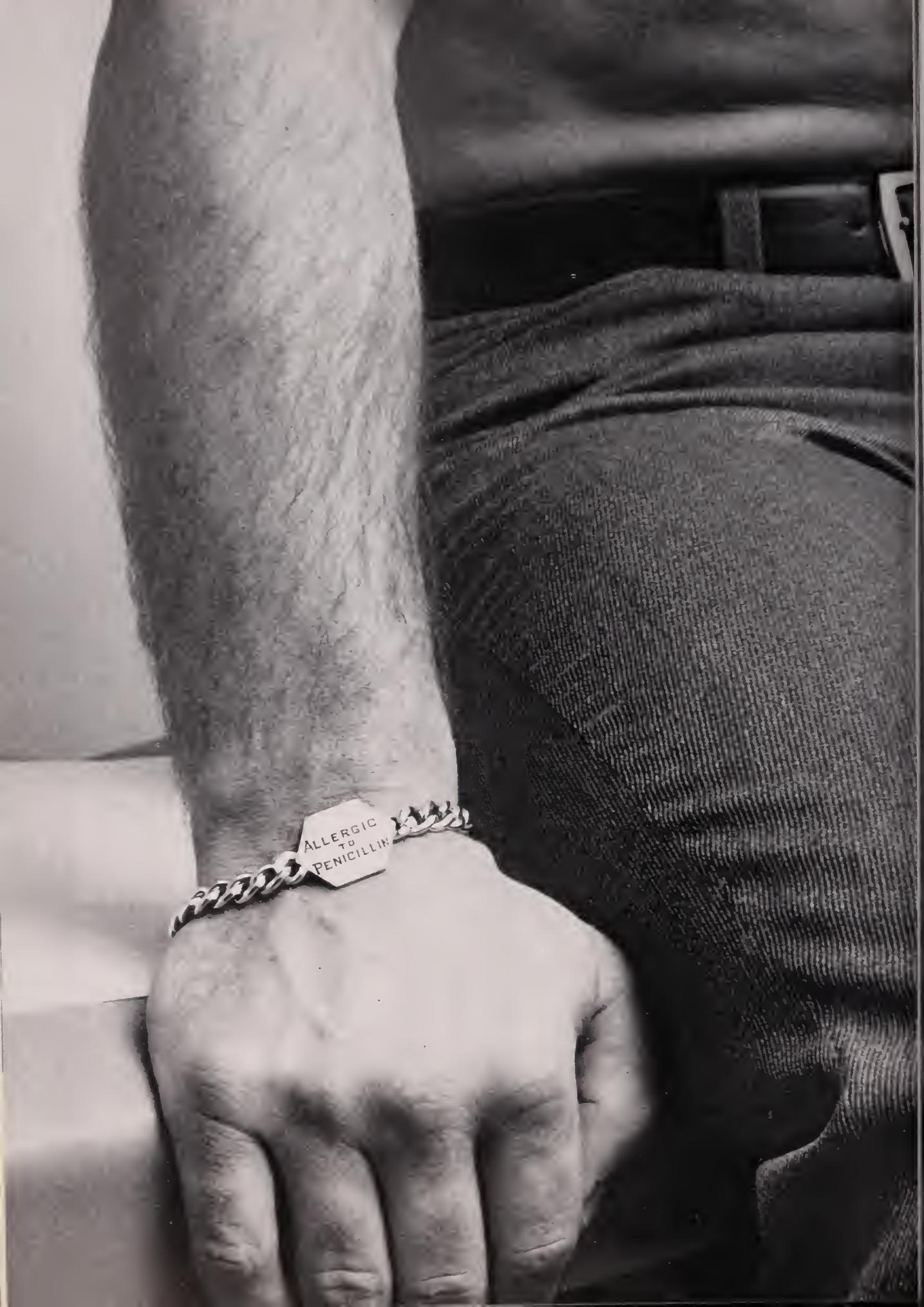
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Brief Summary

Indications

Erythrocin is indicated against gram-positive cocci – staphylococci (most strains), pneumococci and streptococci (including enterococci). Active against other pathogens, such as *Corynebacterium, Hemophilus, Clostridium, Neisseria,* and *Treponema pallidum,* the agents causing trachoma and lymphogranuloma venereum and primary atypical pneumonia caused by *Mycoplasma pneumoniae* (Eaton agent). Establish susceptibility of pathogenic organism when practical. Maintain therapeutic levels for ten days in the treatment of streptococcal infections to help prevent rheumatic fever and glomerulonephritis. Also consider local measures or surgery whenever indicated.

Contraindications

Known hypersensitivity to erythromycin. I.M. preparation also contraindicated in patients hypersensitive to the "caine" type of local anesthetics.

Precautions, Side Effects

Occasionally abdominal discomfort, cramping, nausea or vomiting may occur; generally controlled by reduction of dosage. Mild allergic reactions, such as urticaria and other skin rashes, may occur. Serious allergic reactions have been extremely infrequent; if hypersensitivity is encountered consider appropriate countermeasures, e. g., epinephrine, steroids, etc., and withdraw drug. The rare possibility of overgrowth of nonsusceptible organisms should be kept in mind; if it occurs withdraw drug and institute appropriate treatment. Local venous discomfort, generally mild, may occur with I. V. administration. I.M. preparation is suitable for deep intramuscular administration only; restrict use in children with small muscle mass. A mild transient local discomfort sometimes occurs following rectal insertion of Erythrocin Suppositories; discontinue if significant discomfort persists.

Administration and Dosage

I. ORAL: In adults with mild to moderate infections caused by readily-susceptible organisms 1.0 Gm. daily; more severe infections or those caused by less susceptible organisms 2.0 Grams daily; unusually severe infections up to 4 or more Gm./day. Daily dose in children is 15 to 25 mg./lb./day depending upon severity of infection. Daily dose should be administered in divided doses at 4-to-6 hour intervals. Continue treatment for at least 48 hours after symptoms have subsided and temperature has returned to normal. In fulminating or life-threatening infections, a parenteral form of erythromycin is preferred.

II. PARENTERAL: Intravenous administration may be continuous or intermittent (6 to 8 hour intervals); 1 to 4 Gm. daily in adults; 15 to 25 mg./lb./day in children, depending upon severity of infection. Recommended I.M. dose is 100 mg. (2 ml.) for adults, 50 mg. (1 ml.) for children 30 lbs. or more and 1.4 to 1.8 mg./lb. in smaller children. Injections are usually given at 6 to 8 hour intervals; may be given at 4 to 6 hour intervals for severe infections.

III. RECTAL: Following therapeutic doses are recommended in children: to 20 lbs., 1-125 mg. suppository every 8 hours; 20 to 40 lbs., 1-125 mg. suppository every 6 hours.

Change to oral therapy as soon as practicable.

103305

Classified Advertisements

Classified advertising rates are thirty (30) cents a word; minimum monthly charge $7.50; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

GENERAL SURGEON wanted by young 6-man GP group. College town 30 miles from St. Paul-Minneapolis. JCAH accredited hospital. Reply to J. C. Palmquist, M.D., River Falls Medical Clinic, River Falls, Wisconsin (715) 425-5322.

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ANESTHESIOLOGIST seeks location small city in Minnesota. Age 37, U. S. graduate, Minnesota license. Write Minnesota Medicine—454, 375 Jackson St., St. Paul 55101.

GENERAL PRACTITIONER urgently needed to join a well established practitioner. Excellent hospital and clinic facilities, Greenbush, Minnesota. Salary open and early partnership. Call collect 782-5275 or 782-4725.

GENERAL PRACTITIONER wanted for four man group with Board surgeon associated with community sponsored prepayment plan in NE Minnesota; hay fever haven; accredited hospital with radiologist, pathologist & internist services next door to modern clinic; good schools, swimming pool, indoor ice arena, golf, hunting, fishing, liberal salary $22,000-$25,000 first year; full partnership 6 months; equitable rotating call schedule & immediate work load. Write Medical Director, Community Clinic, Two Harbors, Minnesota 55616.

INTERNIST NEEDED: To join 9-man, all specialty group of 2 Internists, 2 Surgeons, 2 OB/GYN, 3 Pediatricians. City of 40,000 located 1-hour drive from Milwaukee on Lake Winnebago which serves a medical area of 75,000. Single hospital of 350 beds. Area affords excellent summer and winter recreational facilities. Superior schools, public and parochial and 2 colleges. Excellent initial salary leading to partnership in one year. For further information phone or write: W. G. Kendell, M.D., The Sharpe Clinic, S.C., 92 E. Division Street, Fond du Lac, Wisconsin 54935; Tel. (414) 921-0560.

WANTED: General practitioners, Internist, Pediatrician, Orthopedic Surgeon, Obstetrician and Gynecologist for the Bemidji Clinic of Bemidji, Minnesota. Outdoor sports advantage second to none. The Bemidji Clinic now consists of three general practitioners, one internist, two general surgeons, one obstetrician, one otolaryngologist. If interested contact Duane E. Carlson, Business Manager, Bemidji Clinic, Bemidji, Minnesota.

WANTED: GENERAL PRACTITIONER, out of internship or established. Green Bay, Wisconsin (Population 100,000). New clinic for 3 man G-P group. Laboratory, X-Ray, EKG, 2 registered lab technicians, 2 registered nurses, complete office staff. Present partners, ages 57 and 47. Large enough practice for 3 men now. Two Catholic and 1 Protestant hospitals, staff open. Schools both parochial and public are excellent. One university and one college. In heart of boating, fishing, hunting, skiing and snowmobile country. Have symphony orchestra and within easy driving to Milwaukee and Chicago. Jet service daily. Need younger GP to work with us, not for us. Salary open, no investment. We need you badly—two Packer season tickets to sweeten things! Contact R. J. Rose, M.D., or R. E. Jensen, M.D., 621 East Walnut Street, Green Bay, Wis. Call 437-4366.

TEN MAN MULTISPECIALTY group needs an ophthalmologist and another pediatrician. New clinic building, complete laboratory and x-ray facilities. 180 bed modern hospital across street from clinic. Early share-holder status. Salary open. Write or call the Lenont-Peterson Clinic, Ltd., C. A. Tietz, M.D., area code 218, 741-4292, Virginia, Minnesota 55792.

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GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D., Chippewa Falls, Wisconsin.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul 55101.

(Continued to Page 300)

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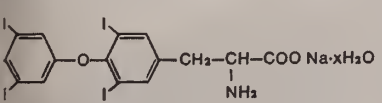
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, F., and Horn, D. B.: Assessment of thyroid function by ombined use of the serum protein-bound iodine and resin uptake of riiodothyronine, J. Clin. Endocrinol. 25:39 (Jan.) 1965.

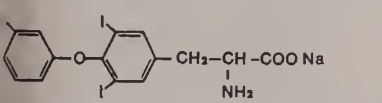
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ons: Euthroid provides replacement ther- for the thyroactive material normally plied by the human thyroid. The normal oid gland produces and stores thyroulin, the active components of which are metabolically active hormones: *l*-thyne and liothyronine. Euthroid (liotrix) pros a combination of these hormones in lied, synthetic form, supplied in a conit 4:1 ratio in order to simulate as closely possible the physiologic and metabolic cts of normal endogenous thyroid secres.

n contrast with the individual synthetic, abolically active hormones, Euthroid will ally produce normal results for PBI, T_3, other thyroid function tests—consistent clinical progress—when persons with ogenous thyroid deficiencies are made nyroid. Sodium liothyronine (T_3) acts more idly and for a shorter period of time than parations of biological origin. Customy, its use as a single agent produces inropriately decreased PBI values. Sodium othyroxine (T_4), on the other hand, is more itly bound by plasma protein fractions and somewhat slower acting than sodium hyronine (T_3); its use as a single agent ds to produce inappropriately elevated values. Euthroid, with its unvarying 4:1 o of T_4/T_3, permits interpretation of appriate laboratory tests consistent with the al clinical status of the patient.

lications: Euthroid (liotrix) provides thyroid lacement therapy in all conditions of inequate production of thyroid hormones, namely:

1) Hypothyroidism, including cretinism and myxedema.
2) Simple (nontoxic) goiter.
3) Subacute or chronic thyroiditis including Hashimoto's disease.
4) Prevention of goiter in hyperthyroid patients undergoing treatment with thiouracil derivatives.
5) Usage in patients who may manifest intolerance to thyroid products of animal origin.

Contraindications: Acute myocardial infarction, adrenal insufficiency, hypersensitivity to any component of this drug.

Warnings: Liotrix should not be used in the presence of cardiovascular disease unless thyroid replacement therapy is clearly indicated. If the latter exists, low doses should be instituted (Euthroid-1/2 or Euthroid-1) and increased by the same amount in increments at 2-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out and adrenal deficiency due to hypopituitarism corrected before liotrix therapy is started.

If hypothyroidism and adrenal insufficiency exist concomitantly, cortisone or similar steroids should be given at dose levels sufficient to correct the adrenal insufficiency before attempting replacement therapy with thyroid hormones.

Likewise, the possibility of alterations in the prothrombin time must be considered and closely monitored in patients on anticoagulant therapy.

Myxedematous patients are very sensitive to thyroid hormones, and dosage should be started at a very low level and increased gradually.

Precautions: Hypothyroid patients are especially sensitive to thyroid preparations, and those with severe hypothyroidism may be unusually so.

Initiation of thyroid replacement therapy in patients with diabetes must be carefully monitored because of potential fluctuation in daily insulin or oral hypoglycemic requirements.

As with all thyroid preparations, this drug will alter the results of thyroid function tests.

Adverse Reactions: Overdosage or too rapid increase in dosage of thyroid preparations can produce signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration: Initial dosage should be low and gradually increased at 2-week intervals until the desired clinical response is obtained.

Laboratory criteria of euthyroidism include a PBI of 3.5 to 8 mcg; T_3, T_4, and BEI tests are useful.

For most patients, a single daily dose of Euthroid-1, -2, or -3 will maintain euthyroidism. Transfer of a patient from a maintenance dose of another thyroid preparation to Euthroid can usually be effected smoothly. See table for initiating therapy or converting from other thyroid preparations.

Euthroid (liotrix)	Approximate Equivalents Natural		Synthetic	
Tablet	T_4*/T_3** mcg	Thyroid USP	T_4*	T_3**
Euthroid-½ pale orange	(30/7.5)	½ grain	.05 mg	12.5 mcg
Euthroid-1 light brown	(60/15)	1 grain	.1 mg	25.0 mcg
Euthroid-2 violet	(120/30)	2 grains	.2 mg	50.0 mcg
Euthroid-3 gray	(180/45)	3 grains	.3 mg	75.0 mcg

*T_4=sodium levothyroxine (*l*-thyroxine)
**T_3=sodium liothyronine (*l*-triiodothyronine)

Dosage for cretinism or severe hypothyroidism in children is the same as for adults with myxedema. Eventual maintenance dosage in the growing child may be higher than in the adult.

Overdosage: *Symptoms*—Headache, instability, nervousness, sweating, tachycardia, and unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm; chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

Treatment — Shock — Supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.

Supplied: Square W/C monogrammed tablets of four potencies, each identified by a different color (see table); bottles of 100 and 1000.

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(Continued from Page 297)

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IMMEDIATE OPENING: Internist or General Practitioner to join six man multispecialty group in northeastern Wisconsin. Excellent professional opportunity to practice in a friendly community, only two actively practicing physicians (General Practitioners) in the community outside of our clinic. Salary commensurate with training and experience first year and then full partnership. Ideal, safe small city living for the family on scenic Lake Michigan with excellent fishing, boating and hunting. All this and still only 1½ hours drive to Milwaukee or 45 minutes to Green Bay or lovely Door County. For complete details contact Robert E. Myers, M.D., Garfield at 23rd, Two Rivers, Wisconsin 54241.

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GENERAL PRACTITIONER—Direct health care program as Staff Physician at state institution located in college city of 40,000, about 65 miles northwest of Minneapolis-St. Paul. 20-bed infirmary on site plus access to facilities of 450-bed local hospital, state hospitals and U. of M. hospitals. Supervise daily activities of nurses, a medical laboratory technician, plus consulting staff including psychiatrist, EENT specialist and others as needed. Area offers easy access to some of the best all-season, outdoor recreational activities in upper Midwest. For particulars call (612) 251-3510 or write, indicating date available and salary requirements, W. F. McRae, Superintendent, Minnesota State Reformatory for Men, Box B, St. Cloud, Minnesota 56301.

STUDENT HEALTH SERVICE—University of Minnesota is seeking a full-time physician who is a generalist or has pediatric training and can relate to college students. This is a clinic-type practice with all specialties represented and offers regular hours, either 9 or 10½ month appointments, and a generous retirement plan. Send resume and salary requirements to Dr. Donald Cowan, Director, University of Minnesota Health Service, Minneapolis, Minn. 55455. An equal opportunity employer.

INTERNIST—Retiring May 1. Equipment and furniture of downtown Minneapolis office for sale. Opportunity to take over established practice if desired. Call office 612-336-7998 or 612-824-9136.

TWO GENERAL PRACTITIONERS, office adjoining Fairview Southdale Hospital, desire doctor to work all or part of June, July and August, 1971. ($500.00 per week plus percentage.) Permanent association possible. Contact: Doctors Krafft and Dornbach, 200 Southdale Medical Building, Edina, Minnesota 55435; Phone: 920-8060 (Area code 612).

EMERGENCY ROOM PHYSICIAN—16-man group in Green Bay, Wisconsin, establishing Emergency Room Department. Positions available. Salary open with available stockholder arrangement. Contact C. G. Novotny, M.D., West Side Clinic, Green Bay, Wisconsin 54303.

ST. LOUIS PARK—new medical suites in Meadowbrook Medical Building directly connected by passageway to the Methodist Hospital. Phone 612-929-2633 Mr. Hirsch, or write Meadowbrook Medical Building, Leasing Office, 6490 Excelsior Boulevard, St. Louis Park, Minnesota 55426.

WANTED LOCUM TENENS: Three-man Minneapolis GP group desires physician with Minnesota license to work parts of the summer of 1971. Salary and conditions excellent. CONTACT 529-9251.

Three Day Symposium

The University of Minnesota School of Medicine, Department of Laboratory Medicine will sponsor a three day symposium on the topic "Streptococcal Disease: Recognition, Understanding and Management" on May 12-14, 1971, at the University.

An outstanding national and international faculty has been recruited for this three day course, which is approved for 18 hours AAGP credit. The fee is $90.00. For information write Dr. John M. Matsen or Dr. Lewis W. Wannamaker, University of Minnesota Hospitals, Minneapolis, Minnesota 55455.

Minnesota State Board of Medical Examiners

Notice is hereby given that a public hearing will be held pursuant to Minnesota Statutes, Section 15:0412, subd. 4, in the above entitled matter in Room 496, Lowry Medical Arts Building, Saint Paul, Minnesota, on Saturday, May 15, 1971, commencing at eleven o'clock, a.m. and continuing until all representatives of associations or other interested groups or persons have had an opportunity to be heard concerning adoption of the proposed rules captioned above by submitting either oral or written data, statements or arguments. Statements or briefs may be submitted without appearing at the hearing.

A copy of the proposed rules is listed below.

State Board of Medical Examiners
J. P. Medelman, M.D.
Secretary-Treasurer

Proposed amendment to ME 2(b)(4)

(4) Evidence satisfactory to the Board of applicant's United States or Canadian citizenship. In the event applicant is not a citizen of the United States or Canada, he shall submit, with his application, evidence that he is a lawful permanent resident of the United States and has made a declaration of intent to become a citizen of the United States. In the event applicant is not legally authorized to make a declaration of intent to become a citizen of the United States, he shall submit, with his application, evidence that the Immigration and Naturalization Service of the United States Department of Justice has approved his petition for a preference visa and granted permission to him to remain in the United States until further notice, awaiting the issue to him of an immigrant visa, which would make him eligible for adjustment of his status to that of a lawful permanent resident.

Proposed new Rules ME 2(g), ME 4(e), ME 5(e), ME 6(f), ME 7(e) and ME 8(f), each of which shall read as follows:

A license issued to an applicant whose petition for a preference visa has been approved is valid only so long as the licensee is a resident of the State of Minnesota, is not valid for the purpose of reciprocity with any other state, territory or country and is conditioned upon: (a) the approved petition remaining in full force and effect, (b) his obtaining the status of lawful permanent resident of the United States as soon as he is eligible therefor, (c) his making a declaration of intent to become a citizen of the United States as soon as practicable thereafter, and (d) his naturalization as a citizen of the United States as soon thereafter as is authorized by the statutes of the United States, and if he fails, neglects or refuses, for reasons within or beyond his control, to become a lawful permanent resident of the United States, to make a declaration of intent to become a citizen of the United States and to become a naturalized citizen of the United States as above set forth, the Board may revoke his license upon proof of the same. A license issued to an applicant who is a lawful permanent resident of the United States and who has made a declaration of intent to become a citizen of the United States is valid only so long as the licensee is a resident of the State of Minnesota, is not valid for the purpose of reciprocity with any other state, territory or country and is conditioned upon his naturalization as a citizen of the United States as soon thereafter as is authorized by the statutes of the United States and if he fails, neglects or refuses for reasons within or beyond his control to become a naturalized citizen of the United States as above set forth, the Board may revoke his license upon proof of the same. Upon the licensee becoming a naturalized citizen of the United States, the restrictions contained in this paragraph shall be of no further force or effect.


2
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Depression is a 24-hour-a-day problem. And insomnia is often its nocturnal expression. In fact, insomnia may be a key symptom in establishing the diagnosis of depression.

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NOTE: Not recommended during the acute recovery phase following myocardial infarction. Patients with cardiovascular disorders should be watched closely; arrhythmias, sinus tachycardia, and prolongation of the conduction time have been reported, particularly with high doses; myocardial infarction and stroke have been reported with drugs of this class. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Concurrent electroshock therapy may increase the hazards of therapy; such treatment should be limited to patients for whom it is essential. Discontinue the drug several days before elective surgery if possible.

Contraindications: Known hypersensitivity. Should not be given concomitantly with or within at least 14 days following the discontinuance of a monoamine oxidase inhibitor. Then initiate dosage of amitriptyline HCl cautiously with gradual increase in dosage until optimum response is achieved. Not recommended during the acute recovery phase following myocardial infarction or for patients under 12 years of age.

Warnings: May block the antihypertensive action of guanethidine or similarly acting compounds. Should be used with caution in patients with a history of seizures or urinary retention, or with narrow-angle glaucoma or increased intraocular pressure. Patients with cardiovascular disorders should be watched closely; arrhythmias, sinus tachycardia, and prolongation of the conduction time have been reported, particularly with high doses; myocardial infarction and stroke have been reported with drugs of this class. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Safe use during pregnancy and lactation has not been established; in pregnant patients, nursing mothers, or women who may become pregnant, weigh possible benefits against possible hazards to mother and child.

Precautions: When used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated; in manic-depressive psychosis, depressed patients may experience a shift toward the manic phase, and paranoid delusions, with or without associated hostility, may be exaggerated; in any of these circumstances, it may be advisable to reduce the dose of amitriptyline HCl, or to use a major tranquilizing drug, such as perphenazine, concurrently.

When given with anticholinergic agents or sympathomimetic drugs, close supervision and careful adjustment of dosages are required. May enhance the response to alcohol and the effects of barbiturates and other CNS depressants. The possibility of suicide in depressed patients remains during treatment and until significant remission occurs; this type of patient should not have easy access to large quantities of the drug. Concurrent electroshock therapy may increase the hazards of therapy; such treatment should be limited to patients for whom it is essential. Discontinue the drug several days before elective surgery if possible.

Adverse Reactions: *Note:* Included in this listing are a few adverse reactions not reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each reaction be considered when amitriptyline is administered.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms. *Anticholinergic:* Dry mouth, blurred vision, disturbance of accommodation, constipation, paralytic ileus, urinary retention, dilatation of urinary tract. *Allergic:* Skin rash, urticaria, photosensitization, edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, parotid swelling. *Endocrine:* Testicular swelling and gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido. *Other:* Dizziness, weakness, fatigue, headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, drowsiness, jaundice. *Withdrawal Symptoms:* Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise; these are not indicative of addiction.

How Supplied: Tablets containing 10 mg and 25 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100, 1000, and 5000; tablets containing 50 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100 and 1000; for intramuscular use, in 10-cc vials containing per cc: 10 mg amitriptyline HCl, 44 mg dextrose, and 1.5 mg methylparaben and 0.2 mg propylparaben as preservatives.

For more detailed information, consult your MSD representative or see the Direction Circular. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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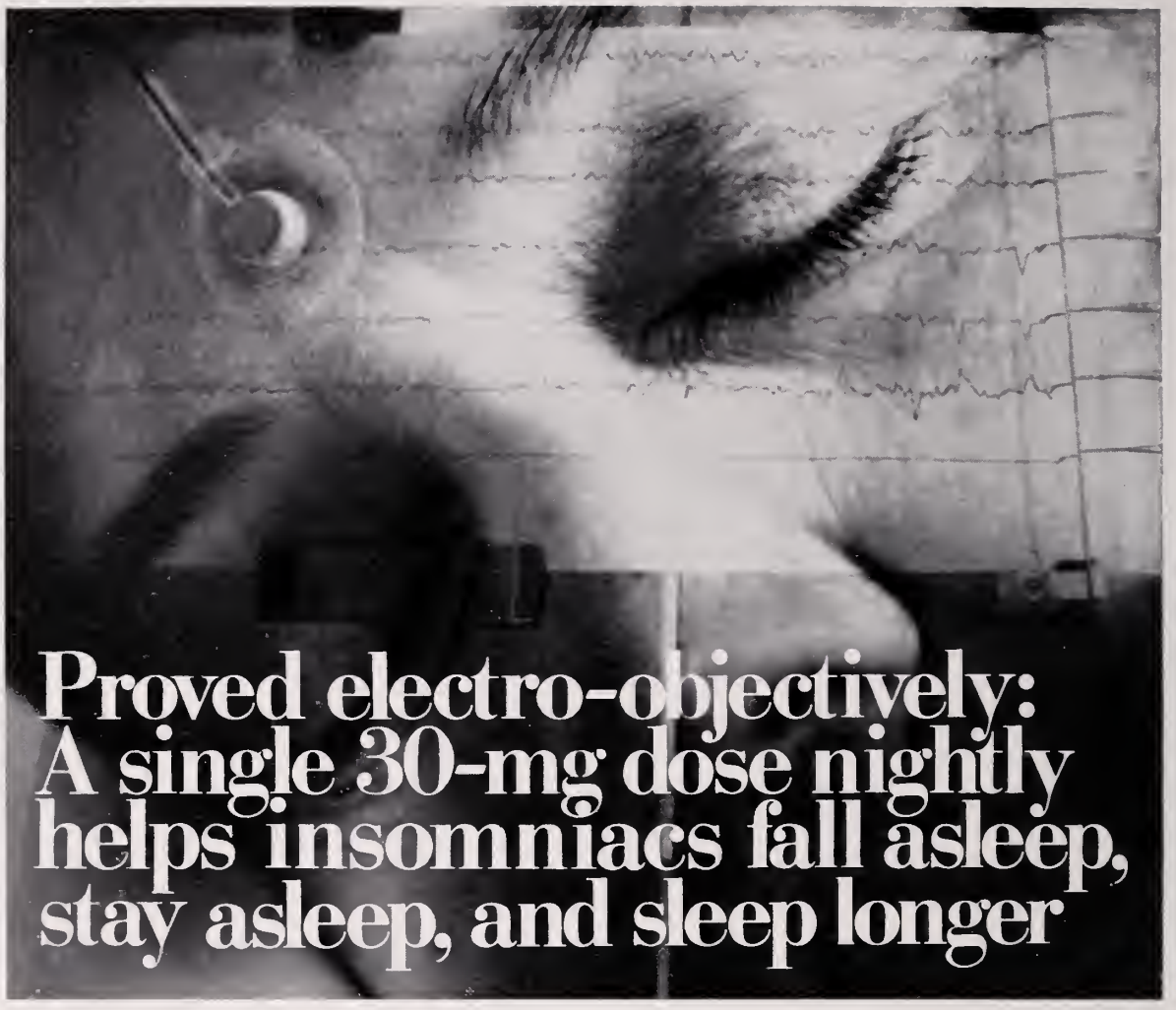
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Controlled studies of 23 insomniac and 13 normal subjects treated with Dalmane (flurazepam HCl) in five sleep laboratories generated over 4000 hours of electroencephalographic, electro-oculographic and electromyographic tracings. These studies revealed that Dalmane 30 mg nightly usually induces sleep in 22 minutes and provides seven to eight hours of sleep.[1,2,3]

Moreover, Dalmane 30 mg was found to be useful in all common types of insomnia in which it was studied. Of drugs studied in a sleep laboratory,[1] Dalmane 30 mg was the only one that consistently reduced sleep induction time and maintained sleep nightly for 14 consecutive nights of use.

Confirmed clinically

Fifty-three controlled studies using a paired-night, double-blind crossover design have evaluated Dalmane clinically. In the majority of these, Dalmane (flurazepam HCl) significantly reduced sleep induction time and increased sleep duration. Dalmane and a placebo were alternated on successive nights in 2010 insomniacs, 1706 of whom were studied for a single night-pair, and the remainder for as many as fifteen paired-nights. A patient preference for Dalmane was apparent in the paired-night studies.

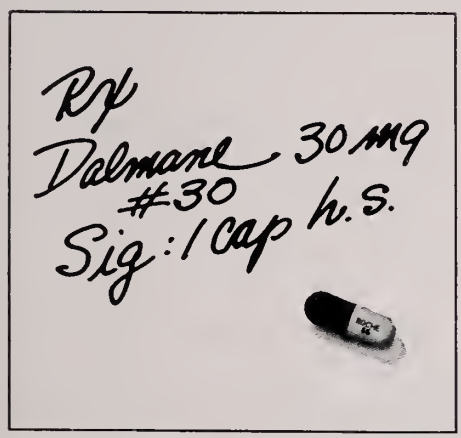
Dalmane was also preferred to certain hypnotics in two separate preference studies. In each of two double-blind studies, Dalmane 30 mg retained effectiveness for the total period of seven consecutive treatment nights, according to subjective/objective evaluations.

In summary, Dalmane is useful in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening. It can be used effectively in patients with recurring insomnia or poor sleeping habits, and in acute or chronic medical situations requiring restful sleep.

Dalmane (flurazepam HCl) is generally well tolerated

In most instances in which adverse effects with Dalmane were reported, they were mild, infrequent and seldom required discontinuation of the drug. Dizziness, drowsiness, lightheadedness and the like were the side effects most frequently noted, particularly in elderly or debilitated patients.[3] Instances of hepatic dysfunction, paradoxical reactions (excitement) and hypotension are rare with Dalmane, and morning hang-over is relatively infrequent. In studies to date the effectiveness of Dalmane for recommended periods of use is maintained without need to increase dosage.

References: 1. Kales, A., *et al.:* "Effectiveness of Sleep Medications: All-Night EEG Studies of Hypnotic Drugs," in Proc. 7th Internat. Cong. Electroencephal. and Clin. Neurophysiol., San Diego, Calif., Sept. 13-19, 1969. **2.** Kales, A., *et al.:* "Psychophysiological and Biochemical Changes Following Use and Withdrawal of Hypnotics," in Kales, A. (ed): *Sleep: Physiology and Pathology,* Phila., Lippincott, 1969, p. 331. **3.** Data on file, Medical Department, Hoffmann-La Roche Inc.



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Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.,* operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.,* excitement, stimulation and hyperactivity, have also been reported in rare instances.

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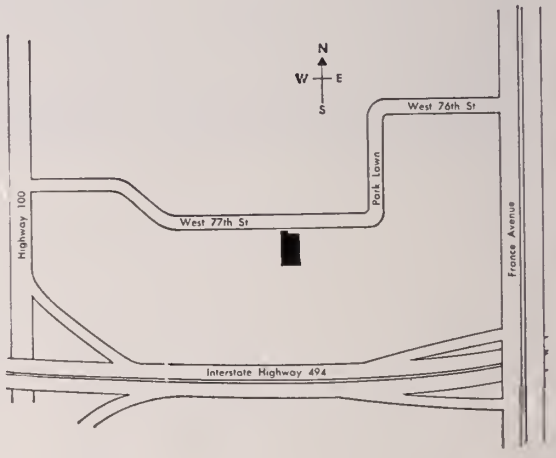
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President's Letter

The Brighter Side

Although several of my Presidential letters appearing in MINNESOTA MEDICINE during the past year have touched on the many social, political and economic problems besetting medicine, there remain some evolving optimistic aspects which should be mentioned.

I beileve, for instance, that student activism on the medical-school campus, as well as in organized medicine, portends well for the future. Enrollment in medical schools in the United States increased sharply last fall, in which the total number in the entering class was 11,360. This was an increase of 938 over the previous year. Minority-group students have increased from 732 to 1,107 in the entering class, and women freshmen medical students increased from 928 to 1,224.

The awareness and acceptance by most physicians of the fact that the consumer does have a role in the economic aspects of medicine, such as support of state medical schools with tax moneys, hospital costs and medical insurance, constitute a desirable advance in rapprochement with the public.

The gradual voluntary trend toward the formation of small groups of three or more physicians to deliver health care in needy areas is all for the good.

The Subcommittee on Standards of Medical Practice, under the leadership of Dr. Jack Falls of Red Wing, has recently completed a one-year feasibility study in which a special in-depth medical audit was conducted by peer-review physicians in each of the seven planning districts throughout the state. At the time of this writing, 33 hospitals and 27 nursing homes have cooperated in the study. Using a standardized audit form, the investigators chose 20 common and comparable diseases for statistical analysis of hospital practice, and a random sample of discharged patients was used for the nursing-home study. Patterns of care emerged which show some striking similarities and some equally striking differences. Federal authorities have expressed great interest in this method of monitoring health-care delivery. Minnesota physicians can be justly proud of this committee and its leadership role. Funds are being sought for continuation of the study.

We physicians in Minnesota can be particularly optimistic because of our well-organized State Medical Association under the direction of our dedicated and indefatigable executive secretary and his staff.

We in Minnesota can be thankful for the concerned, selfless Council of our State Medical Association and of the 61 committees in which some 900 physicians deliberate on many problems facing us in these trying times for medicine.

We in Minnesota can be grateful for having a knowledgeable and articulate incoming president, Dr. Bob Kelly, of Grand Rapids.

R. J. Jackman

Raymond J. Jackman, M.D., President,
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Urinary Appliances and Stomal Care*

DANIEL C. MERRILL, M.D.,† COLIN MARKLAND, M.D.,‡
ELWIN E. FRALEY, M.D.‡

PRESENT METHODS of urinary diversion include: ureterostomy, vesicostomy, and ileac diversion. Regardless of the surgical technique, urine collection and stomal care are important postoperative considerations. Since the family physician frequently participates in the late postoperative care of these patients, it is important for him to have a working knowledge of urinary appliances and be able to diagnose and treat common stomal abnormalities.

The Marlen Appliance

Although there are several acceptable urinary collecting devices, a detailed description of each is unnecessary since the general principles of appliance application pertain to all. The Marlen appliance is discussed because it has had wide acceptance.

The appliance consists of several components¶ (Figure 1). (1) The mounting ring is placed over the stoma. The elastic belt attaches to the knobs on each side, and the disposable plastic pouch attaches to the raised grooved ridge around the center of the mounting ring. The all-flexible mounting ring is usually preferred by adults, while semi-flexible or rigid plastic mounting rings are often more satisfactory for children. The size refers to the center opening which should be 1/16th to 1/8th inch in diameter larger than the stoma. (2) Either the rubber O-ring seal or the plastic lock ring may be used to secure the plastic pouch to the mounting ring. The lock ring makes it possible to change disposable bags with the mounting ring in place on the abdominal wall. (3) Disposable plastic and permanent latex pouches are available. The latter are unacceptable since it is impossible to visualize the stoma through latex, making the appliance difficult to apply and periodic stomal evaluation impossible. (4) The drain-fitting assembly consists of three parts. The body is secured with a rubber band close to the bottom of the bag to make twisting of the outlet impossible when attached to a drainage tube. Two attachments screw into the drain-fitting body. The intermittent drainage screw is used when the bag is to be emptied periodically. The small rubber washer must be inserted between the drainage screw and the drain-fitting body to insure a water-tight seal. The appliance can be adapted for continuous drainage by removing the intermit-

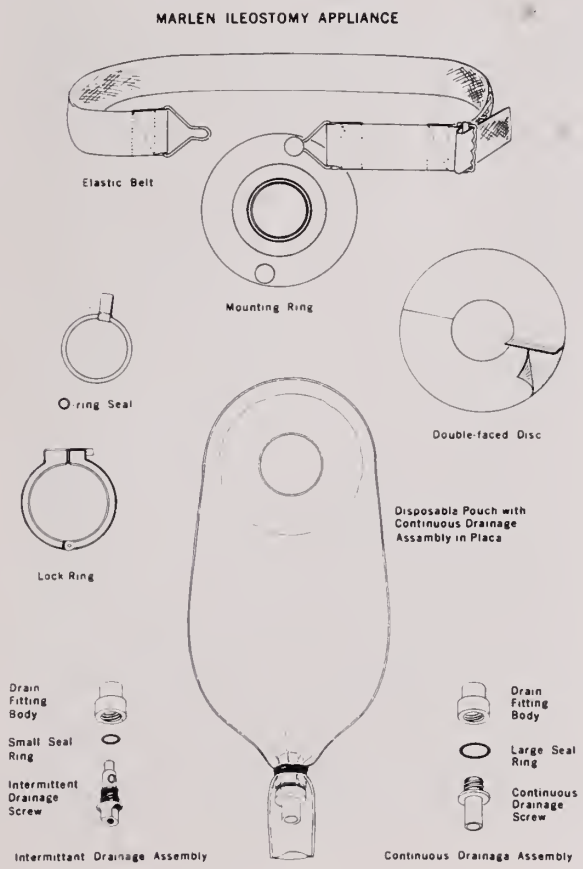


Fig. 1—The Marlen appliance.

*This work was supported by U.S.P.H.S. Training Grant AM 05514 and Special Fellowship AM 45213-01.
†National Institutes of Health Special Fellow in Urology.
‡The Department of Surgery, Division of Urology, University of Minnesota, Health Sciences Center, Minneapolis, Minnesota.
¶A more detailed description of this appliance and a list of other supplies discussed in this monograph can be obtained from the Marlen Mfg. Co., 15150 Richmond Road, Bedford, Ohio.

tent drainage screw and inserting the large rubber washer followed by the continuous drainage screw. (5) Marlen double-faced adhesive discs are used to form a seal between the appliance and the skin. The double-faced disc must cover the inner surface of the mounting ring completely to avoid leaks and skin excoriation. Therefore the diameter of the mounting ring must be determined and stated when ordering the double-faced disc. The double-faced disc is first applied to the mounting ring and the assembled appliance and disc is then applied to the skin. (6) The elastic belt, which is machine washable, holds the mounting ring in place.

Appliance Application and Removal

Proper application requires a clean dry surface to which the double-faced disc can adhere. Residual adhesive material may be removed with benzene, ether or acetone. These agents also remove skin oils which interfere with skin adhesiveness. Alkaline crustations, abrasions, and skin ulcers, must be treated before appliance application. Prior to applying the appliance, benzoin compound, skin bond, or Marlen ileo cement may be applied to the skin, but are usually unnecessary when double-faced discs are used.

During skin preparation a cotton ball is held over the stoma. The cotton ball is removed and the appliance is quickly applied before the surface becomes wet with urine. The appliance may be applied either with the patient sitting up or lying down. The position of the stoma should be checked immediately and, if it is not properly centered, the appliance is removed and reapplied using a new double-faced disc.

To prevent infection and to maintain hygiene the appliance is changed every four to five days even though it continues to stick well. To remove the appliance, the skin is gently pushed away from the mounting ring; if resistance is encountered, the area where the appliance meets the skin surface is brushed with a suitable solvent.

After removing the appliance, the plastic bag and double-faced disc are removed and discarded. The mounting ring, rubber O-ring seal and drainage assembly are washed. The appliance should be cleansed and soaked shortly after removal to prevent odor. Calcium deposits, which may form in the permanent bags, may be removed by soaking in vinegar for one-half hour. If odor is a problem, the appliance may be soaked in O-syl for one-half hour.

Appliance Failure

Improper appliance application is the most common cause of appliance failure. To prevent leaking, the mounting ring must be centered over the stoma. Most patients readily develop

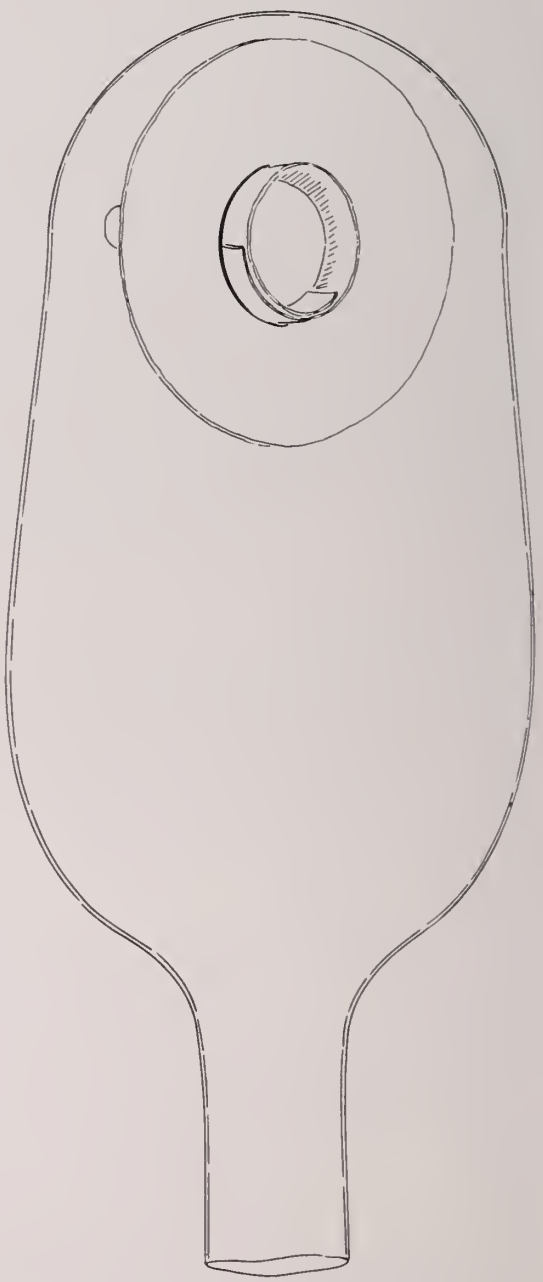


Fig. 2—Mounting ring with stomal guide strip in place.

a method of applying the appliance which accomplishes this purpose. If not, stoma guide strips will facilitate application and insure a perfect fit (Figure 2). After applying the appliance the stoma guide strip falls into the pouch and dissolves.

Wet Skin

Appliance application to a wet skin surface is a frequent cause of leakage. Since a properly working loop intermittently spurts small volumes of urine, it may be difficult to keep the skin surface dry until the appliance is in place. For this reason it is convenient to change the bag in the morning when the patient is dehydrated. If urine wets the surface during application the process must be repeated after the appliance has been prepared with a new double-faced disc.

Custom-Tailored Fitting

An improperly fitting mounting ring with a center hole either too small or too large may also result in urine leakage. As stated, a properly fitting appliance ring will have 1/16th to 1/8th inch clearance between the stoma edge and the inner edge of the mounting ring. Custom-tailored rings can be obtained for eliptical or irregularly shaped stomas. During the first six postoperative months, the mounting ring may have to be replaced several times as the stoma matures and decreases in size.

Skin irregularities caused by scars, abrasions, ulcers, and alkaline phosphate incrustations may result in a poor seal between skin and disc. If such conditions are present, a plastic foam pad may be placed between the skin and the double-faced disc. The foam pad allows the disc to adjust to the skin surface irregularity and thus facilitates union between the disc and skin. If this technique fails and urine leakage persists, the stoma may have to be revised or moved to a site on the abdominal wall which is free of surface irregularity.

Excessive Motion

Lastly, excessive motion often breaks the skin seal. A properly fitting belt, which will stretch three to four inches when attached to the appliance, is important as a tight-fitting belt will pull the appliance from the skin during rapid motion and a loose-fitting belt will give no support. The disc edge may be taped to the skin when the belt cannot be applied because of the approximation of bony prominences.

Stomal Problems

Alkaline Urine

Alkaline phosphate incrustation is the most common stomal complication (Figure 3). As the name suggests, this abnormality is associated with an alkaline urine. If the urine is alkaline, a urine culture is indicated since several organisms which commonly invade the urinary tract produce alkaline urine.

The method of obtaining a urine culture from an ileac loop or a ureterostomy is important as skin contamination must be avoided. The stoma and surrounding skin are washed with aqueous zephiran and a catheter is passed into the loop. For the culture to be valid the patient must be well hydrated and the specimen must be aspirated from the bottom of the loop. A similar technique is used to obtain a urine sample from a cutaneous ureterostomy



Fig. 3—Ileac stoma severely affected with alkaline incrustation.

and the culture is obtained by introducing a small catheter into the ureter and aspirating directly from the renal pelvis. If the urine can be sterilized the pH will often become more acid and the alkaline incrustations will dissolve spontaneously.

Idiopathic alkaline incrustations, which occur in the presence of sterile urine, may be treated by urine acidification; this may be accomplished by a number of oral medications. The incrustations may also be dissolved by placing a 0.25% solution of acetic acid in the pouch or by adding one tablespoon of vinegar to the pouch each time it is emptied. If conservative outpatient methods fail, the patient should be referred to the operative surgeon for possible hospitalization. Since idiopathic alkaline incrustations tend to recur, a prophylactic program consisting of frequent pouch emptying and pouch acidification should be instituted once the stoma is free of incrustations. It is usually sufficient to add vinegar to the pouch once a day under these circumstances.

Yeast Infections

Stomal yeast infections occur. Diagnosis is confirmed by culture and the condition is treated with Nystatin (Mycostatin) Topical Powder. Since this powder is applied three times a day, the lock ring previously described may be used to allow pouch removal and stomal access without separating the mounting ring from the skin.

Bleeding

Stomal bleeding may occur spontaneously or following accidental trauma. The hemorrhage is usually minimal and self-limiting; however, if it does not subside spontaneously, appropriate diagnostic evaluation is indicated, including stomal inspection, loop aspiration, loop-o-gram, loop culture, and intravenous pyelogram. Once the bleeding source is determined, appropriate therapeutic measures may be taken.

Skin Problems

Ulcers

Although skin abrasions and skin ulcers can necessitate hospitalization, usually both can be treated at home under medical supervision. The lesion is washed gently and the surrounding skin cleansed with ether. A paste made of Karaya gum or Protex Powder is then applied to the affected area and covered with paper tape prior to appliance application.

Karaya gum discs may also facilitate healing of small lesions around the stoma. These discs are ordered 1/8th inch smaller than the inner mounting ring diameter. The Karaya gum disc is applied to the double-faced disc before the appliance is placed on the abdominal wall (Figure 4).

Allergic Skin

Allergic skin reactions, although infrequent, can cause severe disability in patients who are allergic to the double-faced discs or other material which comes in contact with the skin. The skin surrounding the stoma ultimately becomes excoriated, making appliance application impossible. The diagnosis is confirmed by patch-testing an adjacent skin area with the double-faced disc or other incriminating material. Minnesota Mining's Stomaseal* and Medical Adhesive B by Dow Corning† are two



Fig. 4—Mounting ring prepared with double-faced disc and Karaya gum disc.

*Minnesota Mining & Manufacturing Co., 3M Center, St. Paul, Minnesota.
†Dow Corning Corporation, Medical Products Division, Midland, Michigan.

non-allergenic adhesive materials which may be used in patients who develop an allergic reaction to other adhesive materials. Preliminary experience with both products has been encouraging.

Miscellaneous Problems

Odor can be avoided if the appliance is changed every four to five days, cleaned properly after removal, and applied properly to prevent leakage of urine. A urine culture is indicated if odiferous urine is present, since it may indicate the presence of urinary infection.

Calcium deposits occur infrequently if the appliance is changed regularly and disposable bags are used. However, if the permanent latex bags are used they must be inspected frequently for calcium deposits, since such deposits are a source of infection, cause odor, and may damage the stoma. Calcium deposits may be removed by soaking the appliance in vinegar.

Most patients become quite independent in the use, care, and application of their urinary appliance. However, continual medical follow-up is necessary, since a poorly functioning loop or ureterostomy may result in severe renal deterioration before the patient is aware of malfunction.

From a Doctor's Journal

November 18, 1886—I was with Mr. Steven D. Boynton last night when he died. He lay breathing heavily, but a little after eleven there was a change. I held my finger on his pulse for about three minutes at the last. His heart seemed suddenly to beat slowly and more slowly like a wheel stopping. The pulse hesitated for a minute as if uncertain whether to stop or go on, as if it were surprised and amazed at the prospect of so great a change. Slowly it vibrated, then seemed entirely gone, but returned again for a few more feeble strokes, after which it was at rest forever.

I could not see what left him, to make so wonderful a transformation. In his external physical appearance there was no apparent difference. His bones, his muscles, his entire body were there, the same, but something had left him, something invisible which had produced a mighty difference. He was no more the same than water is the same as stone, than darkness is the same as light. Mystery of mysteries, the end of life is as marvelous as the beginning. Both are forever unknowable.*

*David S. Kellogg, M. D.: A Doctor at All Hours, edited by Alan Everest, 1970.

Retrieval

In the night of Easter Saturday, 1921, I awoke, and jotted down a few notes on a tiny slip of paper. Then I fell asleep again. It occurred to me at six o'clock in the morning, that during the night I had written down something most important, but I was unable to decipher the scrawl. That Sunday was the most desperate day in my whole scientific life. During the night, however, I awoke again, and I remembered what it was. This time I did not take any risk; I got up immediately, went to the laboratory, made the experiment on the frog's heart . . . and at five o'clock the chemical transmission of nerve impulses was conclusively proved.*

*Otto Loewi (Nobel Prize in Medicine, 1936), as quoted in A Mirror up to Medicine by A. C. Corcoran, M.D., 1961.

Laboratory Letter

An Antibody Test for Rubella

In 1963 and 1964, the largest rubella epidemic the United States has experienced in 20 years swept the country.[1] In Connecticut, for instance, the Director of the Bureau of Preventable Diseases estimated 200,000 cases in a state of 2.5 million people, or two cases for every 25 citizens.[2]

That epidemic left many deaf and retarded children in its wake, and still others with cataracts, small head size, slow motor development, and growth failure. It's hard to say just how many rubella victims exist. Before the 1963-1964 epidemic, Lundstrom, in summarizing 15 reported studies, computed an incidence of malformations at 33%, 25%, 9%, and 4% in infants whose mothers had rubella in the first, second, third, and fourth months of pregnancy.[3] But in a study of Baltimore children stricken in 1963 and 1964, Dr. Janet Hardy, a Johns Hopkins pediatrician, put the incidence of malformations at nearly 90% in the first trimester and 15-20% in the second trimester.[4] Because rubella epidemics tend to occur in seven-year cycles, authorities expect a new wave of cases in 1970 or 1971.

Therefore you may want to screen certain persons for evidence of past or present rubella infection: pregnant women for their susceptibility to rubella, so that you can determine the need for vaccination in the postpartum phase; women exposed to or suspected of having rubella in the first or second trimester, so that you can document the disease and explain its consequences; or children with a rash, so that you can distinguish rubella from other viral exanthems.

The hemagglutination-inhibition rubella test requires 1 ml. of serum (or 5 ml. of whole blood if you have no centrifuge). If the patient has no current rubella exposure or infection, an antibody titer of 1:10 or greater indicates immunity. If the titer is less than 1:10, the patient is susceptible to rubella, i.e., *not* immune. If she has been exposed or has a rash, try to take a blood sample within a week (preferably three or four days) after exposure or after onset of rash; then draw a second specimen three or four weeks later. If the titer increases fourfold, you can assume (and report) a rubella infection. If both titers are low, the patient is probably not immune. If both are high, the patient has probably had past exposure to rubella.

Richard Reece, M.D.
Minneapolis, Minnesota

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4. Rubella Study Puts Defect at Almost 90%, Medical World News, September 29, 1967.

A woman visitor to the London Zoo asked a keeper whether the hippopotamus was a male or a female.

"Madam," replied the keeper sternly, "that is a question that should be of interest only to another hippopotamus."*

*Julian Huxley

Clues to Discovery of Pulmonary Tuberculosis

DAVID T. CARR, M.D.,* ALFRED G. KARLSON, Ph.D.,† and
W. EUGENE MILLER, M.D.‡

REMARKABLE PROGRESS has been made toward the eradication of tuberculosis in the last 20 years. The new case rate in Minnesota has decreased from 134.8 per 100,000 in 1948 to 10.0 per 100,000 in 1968[1] (Table 1). Nevertheless, the disease remains a challenging medical problem because of its contagious and curable nature. Not only can the dissemination of infection in the community be stopped, but the individual patient can be cured of the disease as well.

TABLE 1
New Case Rate of Tuberculosis in Minnesota

Year	New Case Rate*
1948	134.8
1953	68.2
1958	34.7
1963	19.9
1968	10.0

*Per 100,000 population.

The records of 100 consecutive cases of newly diagnosed pulmonary tuberculosis (the most common and contagious manifestation of tuberculosis) were reviewed to determine the clues that led the physician to suspect the presence of the disease. Only cases in which proof of *Mycobacterium tuberculosis* was obtained from bronchopulmonary secretions or from resected lung tissue were accepted for this study.

*Mayo Clinic and Mayo Foundation: Section of Medicine.
†Mayo Clinic and Mayo Foundation: Section of Microbiology.
‡Mayo Clinic and Mayo Foundation: Section of Roentgenology.

TABLE 2
Age and Sex of 100 Patients With Pulmonary Tuberculosis

Age, yr	Female	Male	Total
0-19	1	2	3
20-39	8	13	21
40-59	17	23	40
60+	8	28	36
Total	34	66	100

Results

The disease was detected in patients of every age group of both sexes (Table 2) and of many occupations (Table 3).

TABLE 3
Occupations of 100 Patients With Pulmonary Tuberculosis

Occupation	Female	Male
Housewife	21	0
Retired	0	13
Executive	0	13
Skilled laborer	0	13
Office or sales worker	7	8
Physician	1	7
Teacher	1	2
Miscellaneous	4	10
Total	34	66

Early Symptoms and Signs

The importance of the routine roentgenogram of the thorax as an initial clue is clearly demonstrated; roentgenographic evidence was the first clue in two thirds of the patients (Table 4). A symptom of pulmonary tuberculosis was the initial clue in almost one third; cough, expectoration of mucoid and purulent sputum, and hemoptysis were the most common. Contact with an infected person was an infrequent initial clue. This may be because few patients come to the Mayo Clinic for examination after possible contact since such examinations are usually carried out by local health departments. The physical examination was relatively unimportant in the discovery of pulmonary tuberculosis.

TABLE 4
Initial Clues to the Diagnosis of Pulmonary Tuberculosis

Clue	Female	Male	Total
Roentgenogram	20	45	65
Symptoms	11	18	29
Contact with another patient	3	2	5
Physical examination	0	1	1
Total	34	66	100

Laboratory Findings

Results of other examinations generally believed to be of value in the study of tuberculosis were analyzed. The sedimentation rate had been measured in 82 patients. Forty-one had rates of 30 mm or less in one hour, 15 had rates of 31 through 60 mm, and 26 had rates of more than 60 mm. The temperature had been recorded in 91 cases and was above 100 F in only eight. The hemoglobin concentration had been measured in all but one patient and was more than 12 gm/100 ml in 84. Eleven patients had 10 to 12 gm, and four had less than 10 gm. The leukocytes had been counted in 98 cases; the count was less than 4,000/cu mm in four, 4,000 to 8,000 in 52, 8,000 to 12,000 in 39, and more than 12,000 in only three. None of these results was of much help in the evaluation of these patients with pulmonary tuberculosis.

Tuberculin Test

In the 75 patients who were tested at the Mayo Clinic, the results of the tuberculin test commonly used to detect tuberculosis infection show that the test is accurate, provided the larger dose of purified protein derivative is used for a second test when there is no reaction to the smaller first dose (Table 5).

TABLE 5
Results of Tuberculin Tests of 75 Patients With Pulmonary Tuberculosis

Dose of PPD, mg	Positive	Negative
0.0001	65	10*
0.005	5	0

*Of the 10 patients who had negative reactions to 0.0001 mg of PPD, only 5 were retested with 0.005 mg of PPD, and all 5 had positive reactions.

Roentgenogram

Analysis of the roentgenogram of the thorax (the most important clue to the discovery of pulmonary tuberculosis) revealed two without any evidence of abnormality, 10 with evidence typical of nontuberculous pulmonary disease, 23 showing inactive pulmonary tuberculosis, and 65 with findings typical of active pulmonary tuberculosis. These data indicate that tuberculosis has to be considered in the differential diagnosis of almost any pulmonary disease but reveal that the roentgenogram is inadequate in differentiating active from inactive pulmonary tuberculosis.

Summary and Conclusions

Data from 100 consecutive cases of newly diagnosed, active, pulmonary tuberculosis were reviewed to determine the clue that led to the diagnosis. The roentgenogram of the thorax was the initial clue in 65, the presence of symptoms in 29, contact with an infected person in five, and the result of physical examination in only one. Analysis of the roentgenograms revealed great variations in the lesions, with only 65 roentgenograms showing evidence of active pulmonary tuberculosis.

A roentgenogram of the thorax should be a part of every general examination and of almost all examinations that are of limited extent. All abnormalities should be carefully evaluated, and tuberculosis should be considered in the differential diagnosis. The roentgenographic appearance is frequently misleading in the determination of activity of the disease, because cultures for *Mycobacterium tuberculosis* may be positive in patients with apparently healed fibrocalcific lesions.

Because pulmonary tuberculosis is both contagious and curable, physicians should continue to search for evidence of the disease in all patients.

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Dr. Joseph J. Kline smiled at a little fellow after completing a pediatric examination. "And, Michael, what are you going to do when you get to be as big as your mother?"

*"Diet," answered the boy.**

*Dr. Francis Leo Golden: Jest What the Doctor Ordered.

Pulmonary Infiltrate

Initial Manifestation of Toxoplasmosis*

B. J. KENNEDY, M.D.† and ATHANASIOS THEOLOGIDES, M.D., Ph.D.‡

TOXOPLASMOSIS IN THE adult is of increasing significance as an opportunistic infection in patients with advanced malignant neoplasms and auto-immune diseases. This disease and other protozoan, fungal, and viral infections are being noted more frequently during the administration of corticosteroids, cytotoxic chemotherapy, radiation therapy, or other immunosuppressive therapies in the treatment of these immunological deficiency states or following organ transplantation. Since new therapies are available for some of these opportunistic infections, the early clinical recognition of the disease may be tantamount to survival of the patient.

Toxoplasmosis produces a variety of clinical manifestations; it may involve many systems or remain localized. On this basis, the disease has been classified into glandular, miliary, and localized.[1] Toxoplasmosis may be clinically manifested as a disease of one organ only, subsequent autopsy confirming the fact that this single organ is involved. This type may result from a previous subclinical or clinically disseminated but unrecognized toxoplasmosis. Two of our patients with multiple myeloma have died of the disease. In one, there was cerebral toxoplasmosis and in the other, a meningitis due to *Toxoplasma gondii*. In both patients there was a previous history of pulmonary infection, and it is suggested that this pneumonitis may have been the original manifestation of toxoplasmosis. Furthermore, the lack of a high titre of the Sabin-Feldman dye test would suggest suppression of an immune response in patients receiving immunosuppressive therapies.

Case Reports

Case 1.

This 55-year-old woman had been fatigued for two years, with chest and back pain for 18 months. The bone marrow contained 34 per cent plasma cells. Fractionation of serum protein by paper electrophoresis demonstrated a homogenous protein peak of 5 gm per 100 ml, which migrated as a slow gammaglobulin component. The total protein was 11 gm per 100 ml. Roentgenograms re-



Fig. 1—Case 1. Bilateral pulmonary infiltrate at the acute phase of infection.



Fig. 2—Case 1. Resolution of pulmonary infiltrate seven weeks after the acute infection.

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vealed multiple osteolytic lesions. Treatment for multiple myeloma was begun with a combination of oral cortisone, 25 mg, urethane, 0.3 gm, and chlorambucil, 2 mg three times a day, with resulting subjective improvement.

After 11 months of therapy a respiratory infection occurred. A chest x-ray revealed linear infiltrates radiating bilaterally from both hila (Figure 1). Tetracycline was administered for 10 days. The pulmonary infiltrates resolved slowly over two months (Figure 2).

During the subsequent two years the patient did well. After 18 months of therapy, the myeloma peak of the serum electrophoretic pattern disappeared, and the plasma cells in the bone marrow decreased to 1.2 per cent.

Three years after the onset of chemotherapy, the patient was readmitted to the hospital because of a three-week history of malaise, lethargy, occipital headaches, and increased bone pain. Neurologic examination did not elicit focal or generalized abnormalities. The total serum protein was 6.8 gm per 100 ml with 4.2 gm of globulin. The patient became more lethargic and complained of nausea, headaches, and generalized weakness. The right biceps reflex became more active, and the Babinski reflexes were positive bilaterally. An electroencephalogram showed a marked diffuse abnormality with generalized slowing and multifocal spikes in the posterior region. The cerebral spinal fluid was clear with an opening pressure of 230 mm of water and six cells per cmm, protein 135 gm per 100 ml, and glucose 45 mg per 100 ml. The patient died seven weeks after admission.

Postmortem examination of the brain revealed large defects in the internal capsule, thalamus, midbrain, and cerebellum. These areas were soft with some hemorrhages in the center.

Microscopic examination revealed large areas of necrotic tissue in both hemispheres. Within and adjacent to such lesions, there were moderate numbers of 1 to 3 micra, gram-negative organisms that were generally free within the tissue, but occasionally located within well-defined cysts. These organisms had the appearance of *Toxoplasma.*

Case 2.

This 63-year-old man had a three-month history of rib and back pain, weakness, weight loss of 20 pounds, and a low-grade fever. The serum electrophoretic pattern revealed a serum albumin of 4 gm per cent and a gammaglobulin of 0.3 gm per cent. The total protein was 6.6 gm per cent. In the urine there was a monoclonal peak. Immunoelectrophoresis of the serum revealed a decrease of the 7S gammaglobulin but large amounts of free L-chain of lambda type in the serum. The hemoglobin was 9 gm per 100 ml, blood urea nitrogen 25 mg per cent, and serum calcium 10.3 gm per cent. The stool urobilinogen was elevated at 356 Ehrlich units per cent. Roentgenograms revealed multiple osteolytic lesions consistent with multiple myeloma. The bone marrow examination showed 6.2 per cent plasma cells.

The upper thoracic spine was treated with 2,600 r of radiation therapy. Concomitantly, testosterone enanthate, 400 mg twice a week intramuscularly, prednisone, 30 mg daily, and cyclophosphamide, 150 mg daily by mouth were given. The patient became more alert, had pain relief and, with the support of a back brace, was able to move about.

Three months after therapy was initiated the patient began to have cough and night sweats. Two weeks later he was readmitted to the hospital acutely ill with a temperature of 103°F. There were vesicular lesions about the lips, chin, and nose. The oral mucosa was covered with white plaques.

The white blood count was 1,350 with 95 per cent neutrophils. The chest roentgenogram revealed extensive bilateral infiltrates over the entire lung fields (Figure 3). The complement fixation tests for histoplasmosis, blastomycosis, coccidiomycosis, and psittacosis were negative. Cold agglutinins were absent. Blood cultures were sterile and sputum cultures revealed no acid-fast bacilli. Cell blocks of the sputum were negative for malignant cells and no cytomegalic inclusion bodies or pneumocystis carinii organisms were seen. Mycoplasma organisms were absent in sputum cultures.



Fig. 3—Case 2. Extensive bilateral pulmonary infiltrates at the onset of the acute infection of toxoplasmosis.

It was concluded that the patient had a stomatitis related to the leukopenia and most likely a viral pneumonia associated with the herpes simplex. Cyclophosphamide was discontinued, transfusions were administered, and the androgen and prednisone were continued. The patient gradually improved. One month later the chest x-ray had improved and the patient was subjectively well. There was no cough and respirations were normal. Cyclophosphamide therapy was reinstituted at 50 mg daily. Three months after the initial pulmonary changes the roentgenograms still revealed evidence of an infiltrate in both lungs (Figure 4). The Sabin-Feldman dye test for *Toxoplasma* antibodies was positive in a serum dilution of 1:64. The complement fixation tests were negative. Five months after the initial pulmonary changes the patient felt well and had gained weight; the hemoglobin had increased to 14 gm per cent. One month later the *Toxoplasma* dye test had decreased to 1:16. After seven months the roentgenograms of the chest demonstrated normal lungs (Figure 5). For the next five months he remained well.

Fifteen months after the initial diagnosis of multiple myeloma the patient noted a gradual decrease in appetite, weight loss, and fatigue over a one-month period.

He was readmitted to the hospital because of five days of progressive weakness of the left foot and leg, weakness of the left arm, and slurred speech. There was fever, a left central seventh nerve paresis, hyperactive reflexes on the left with unsustained ankle clonus, and a positive left Babinski reflex. There was decreased strength of the left arm and leg and mild sensory loss in the left leg. The neurological examination suggested a lesion in the internal capsule. The brain scan, electroencephalogram, right carotid angiogram, and lumbar puncture were normal. During the first five days of hospitalization there was a rapid progression to a complete left hemiplegia.

The hemoglobin was 10 gm per cent, blood urea nitrogen 21 mg per cent, and serum gammaglobulin 0.2 gm per cent with a total protein of 5 gm per cent. Blood and urine cultures were negative; no fungi were noted in the spinal fluid, sputum, or endotracheal cultures. The bone marrow examination revealed a slightly hypocellular marrow. In a differential of 2,000 cells there were 0.4 per cent plasma cells. A diagnosis of multiple myeloma could not be made. Because of the clinical consideration of the diagnosis of a brain abscess due to toxoplasma, a Sabin-Feldman dye test for *Toxoplasma* antibodies was done. The result was 1:16. The dye test on the spinal fluid was negative.

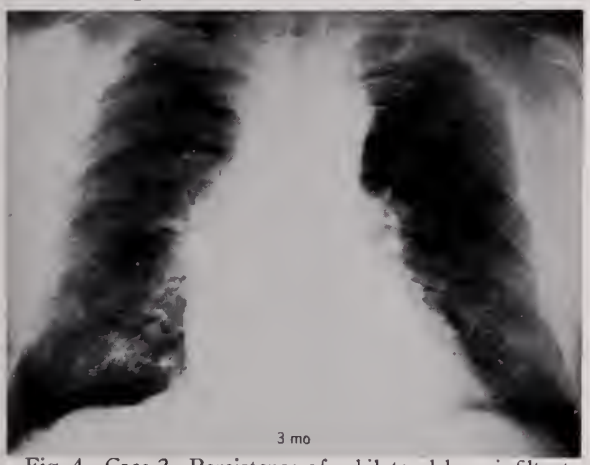


Fig. 4—Case 2. Persistence of a bilateral lung infiltrate three months after the acute infection.



Fig. 5—Appearance of the chest roentgenogram eight months after the initial pulmonary infection.

The patient expired three weeks after admission and 17 months after the initial diagnosis of multiple myeloma. Postmortem examination revealed patches of hemorrhagic consolidation in the left lung and upper lobe of the right lung. Imprints of the lung tissue stained with Giemsa's stain and silver methenamine did not disclose any specific organisms. The bones of the skull, vertebrae, and ribs were soft; microscopic lesions of multiple myeloma were present. The heart was enlarged and weighed 550 grams. A few foci of round cells and histiocytes were noted in the heart. In the cytoplasm of occasional myocardial cells near an area of inflammation, there were nucleated organisms resembling *Toxoplasma gondii.*

On coronal section through both cerebral hemispheres there were petechial hemorrhages and slightly yellowish, discolored, ill-defined lesions in the right globus pallidus, right basal ganglia, right thalamus, roof of the anterior extremity of the left temporal horn, brain stem, and pons. Microscopically, these lesions showed frank necrosis of the parenchyma and occasional vessels, petechial hemorrhages, and numerous small nucleated organisms resembling *Toxoplasma gondii,* widely scattered singly within and about areas of necrosis and occasionally present in pseudocysts.

Discussion

Toxoplasma infections occur throughout the world with varying prevalence. Population studies have revealed positive dye tests in a high per cent of people eating undercooked or raw meat. There is little acceptable evidence that infection is regularly transmitted from human to human.[2] Most human infections appear to be acquired by the oral route, followed by parasitemia, dissemination, and resolution. The parasite is widely distributed in its host and remains viable in cysts in his tissues perhaps for as long as he lives. Generalized toxoplasmosis can be anticipated whenever the host's immunity status is markedly disturbed by immunosuppressive chemotherapy.

Two patients with multiple myeloma died of central nervous system toxoplasmosis. The course of the multiple myeloma was characterized by administration of immunosuppressive anti-tumor therapy and adrenocorticosteroids. A pulmonary infection characterized by fever, cough, and bilateral diffuse pulmonary infiltrates occurred one and two years before the death of these patients. This pulmonary infection, although resembling a viral pneumonia, was unique with respect to the diffuse aspect of the infiltrate, the prolonged period of the presence of abnormal chest roentgenogram changes, and complete slow resolution of the pulmonary infiltrates over a period of two and three

months.

In the first patient, a diagnosis of toxoplasmosis was made on autopsy examination.[3] In the second patient, the characteristic pulmonary lesion resembling that of the first resulted in the demonstration of a positive Sabin-Feldman dye test for toxoplasma antibodies. The subsequent clinical manifestation of left hemiplegia and progressive lethargy resulted in a clinical diagnosis of a brain abscess due to *Toxoplasma*, confirmed by autopsy.

First Recorded Cases

Among the first recorded cases of toxoplasmosis acquired in adult life, Pinkerton and Henderson reported two in which interstitial pneumonia was prominent and contributed to the fatal outcome.[5] There was fever, dry cough, dyspnea, cyanosis, and rales over both lung bases. The hilar shadows were prominent and lung markings were present throughout both lung fields, accentuated at the bases. Death was due to interference of respiratory function. Autopsy examination revealed interstitial pneumonitis and intracellular parasites in the alveolar lining cells.

Sante reviewed the roentgenograms of the two patients reported by Pinkerton and Henderson[6] and suggested that the roentgen picture of toxoplasmosis may simulate atypical pneumonia, mycotic infections, or psittacosis.

Our two cases emphasize the slow resolution of the roentgen picture. Eysell and Steinbruck reported a patient with a febrile illness and a positive Sabin-Feldman test in whom it took a total of 12 weeks before the x-ray findings were within normal limits.[7]

Armstrong and MacMurray reported a patient with atypical pneumonia who had a high dye test titre for *Toxoplasma* and a localized lymphadenopathy from which *Toxoplasma* was isolated by animal inoculation. The roentgenogram showed slight diffuse haziness of both lungs.[8] Other investigators reporting single cases of toxoplasmosis have noted mild lung involvement or interstitial pneumonitis.[4,9-12] In reviewing 21 published fatal cases of toxoplasmosis in children and adults, Hooper recorded five with pseudocysts in the lungs and 18 with inflammatory lesions. *Toxoplasma* lesions were most frequent in the heart, then in the brain, and often in the lung.[13] Ludlam and Beattie have reported eight cases of respiratory disease in adults lasting two to 16 weeks, which possibly represented pulmonary toxoplasmosis. In one of these patients, *Toxoplasma* was demonstrated following animal inoculations with the suspension of the patient's lung.[14] Jacobs described the occasional occurrence of mild pulmonary infiltration in acute *Toxoplasma* infection. As the disease grades into its much rarer and severer form, pneumonitis is a striking sign.[15]

A prolonged period between the initial infection and the acute or fatal process has been suggested. Stanton and Pinkerton in a case of glandular toxoplasmosis in a 26-year-old woman thought that an atypical pneumonitis, which cleared slowly at the age of 11 years, might have been the initial infection.[16] In Espersen's case, the patient showed signs of progressive pulmonary disease during a number of years, reticular hyperplasia similar to that of toxoplasmosis in a lymph node, and high dye test titres.[17] The reports suggest that toxoplasmosis is a rather frequent disease in adults, but that the inconspicuous symptoms rarely permit clinical diagnosis.[18] Pulmonary involvement is common in cases of congenital and severe generalized toxoplasmosis, but it is rare as an isolated process.[11]

The occurrence of a diffuse bilateral pulmonary infiltrate associated with fever and cough in patients receiving immunosuppressive therapies and in patients with multiple myeloma with impaired immunological responses warrants the consideration of a diagnosis of toxoplasmosis. In the evaluation of the pulmonary disease, the Sabin-Feldman dye test and complement fixation test for *Toxoplasma* antibodies should be obtained along with other complement fixation tests for fungal infections. A rising or falling titre is indicative of infection by *Toxoplasma*. The use of immunosuppressive therapies may interfere with antibody formation. As a result the dye test may not be as elevated as in ordinary cases of toxoplasmosis. Nevertheless, elevations of 1:16 and 1:64, as in our cases, are indicative of the presence of the organisms and substantiate the clinical diagnosis of toxoplasmosis. Despite the presence of *Toxoplasma* meningitis, the spinal fluid dye test was negative. This would substantiate further the concept that the immune response

mechanisms were suppressed, possibly by the chemotherapy. Since toxoplasmosis is potentially a treatable disease with pyrimethamine and triple sulfonamide therapy, the clinical recognition of the initial infection substantiated by the Sabin-Feldman dye test may provide for earlier treatment with prevention of subsequent localized toxoplasmosis.

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Doctors Expensive?

A doctor, picking up his car at a garage, was highly indignant at the size of the repair bill. "All this for a few hours' work!" he yelped. "Why, you charge more for your work than we of the medical profession do!"

"Well now," drawled the mechanic, "the way I look at it, we got it coming to us. You guys have been working on the same old model since time began, but we gotta learn a brand-new model every year."*

*Readers Rigest

Take Time

If an executive hasn't enough sense to take care of his own health, he hasn't enough sense to supervise other people, commented the head of a large Midwestern company. Recent survey of five hundred apparently healthy business leaders showed 41% suffered from ailments of which they were unaware; 71% had some physical abnormality; 52% were in need of immediate treatment; 11% "knew something was wrong" but "didn't have time to seek medical advice."*

*Newsweek.

A wonderful discovery—psychoanalysis. Makes quite simple people feel they're complex.—S. N. Behrman

A Tired Doctor's Prayer

When I, having finished with things below,
Lie out 'neath the sod alone,
Raise no cold monument to me
Of brass or bronze or stone.

But plant me beneath a big oak tree,
With its roots firmly fixed in the sod,
And its branches pointing everywhere
To the throne of the living God.

Plant me out in the open on some fair hill
And not in a burying ground;
'Twould be hard for me I know to keep still
With other folk lying around:

And if you can manage a glimpse of the Bay,
Where the white sails shake in the sun,
I know I'll be far more willing to stay—
I always did love a gun.

But I 'spose that shooting will be forbid
Unless you've got a pull,
Why? on account of the brimstone, Kid!
That stuff's inflammable.

And there is the Spring, the birds will come
In the sun and the April rain,
And I know that I'll know when the soft winds blow
And Old Earth is alive again.

I'll hear the birds twittering their love in the morn:
And at night, ere they sink to rest,
They'll tell me that Earth has been reborn
In a way that is God's very best.

I'll see again that tender haze
That comes with the Spring so fair:
And Oh, how I'll love the long, long days,
For I shall have never a care.

The telephone will be silent, mute,
The door bell will be quite dumb,
And I'll never respond to the fool galoot
Who is calling for me to come.

But I'll rest and rest through the silent days,
With no clock or silver chime
To remind me about my wasteful ways
Or hint that it's "getting up time."

When Bob with appendicitis is took,
Or Jim has a broken jaw,
I a Doctor, I'll never give him a look,
I'll be cool as a mother-in-law.

When the baby has eaten carbolic salve,
Or swallowed a safety pin,
There won't be a single thing that I'll have
To do but keep quiet and grin.

Oh God! for a day or two of rest
Away from all sickness and sin,
Where soft winds blow the hours out of the West,
That cool dawns have wafted in.

Yes, plant me beneath a big oak tree
Wide spread to each wind that blows!
If there is none to be found, plant a young one on me
I'll have time to wait while it grows.

---

*Every physician yearns for the day when he can put his worn bag in the closet, throw away his newest surgical blade and retire quietly to some retreat where he can write those treatises on his medical observations which he had longed to do.

George David Stewart (1862-1933) summed up all that longing in one poem, written for the Charaka Club—A Tired Doctor's Prayer.

Born in Cumberland County, Nova Scotia, Stewart was educated at St. Francis Xavier College and was graduated from Bellevue Hospital Medical College as a Doctor of Medicine in 1889, later interning there before becoming Professor of Surgery, and later practicing in New York.

Desquamative Interstitial Pneumonia

A Form of Muscular Cirrhosis of the Lung
Fibrosing Alveolitis*

HANS KUISK, M.D., D.SC.† and JOSE S. SANCHEZ, M.D.‡

In 1963 the authors performed a postmortem examination on a 56-year-old white male who had had, for several years, a history of progressive respiratory distress with a non-productive cough. He died of cor pulmonale. His chest roentgenogram showed a heavily reticulated pattern with a honeycombed appearance (Figure 1). His lung surface was extremely nodular, resembling the liver in Laennec's cirrhosis. Cut sections showed a carnified lung with multiple cysts, more prevalent in the periphery. The microscopic slide (Figure 2) revealed these cysts to be bronchiolectatic dilatations, mainly involving the terminal bronchioles. Proliferation of smooth muscle was noted (Figure 3). This disease was recognized to be the same as one of our previously observed cases of the rare muscular cirrhosis of the lung (Figure 4). The literature revealed less than 30 such cases.

The first description of this disease was credited to von Buhl back in 1872.[3] It had been reported as cirrhosis cystica pulmonum,[23] pulmonary muscular hyperplasia,[24] bronchiolar emphysema,[28] and idiopathic diffuse bronchiolectasis.[10,15] To our surprise we found no reference in these reports to another similar disease, the chronic form of Hamman-Rich syndrome. However, we could find no difference between these two diseases, either clinically, roentgenographically or histopathologically. Later we found that this belief had been previously expressed by others[5,11,20] but had entirely escaped general attention.

*From the Departments of Radiology and Pathology, University of Minnesota and Veterans Administration Hospital, Minneapolis. Presented at the 12th International Congress of Radiology in Tokyo, third of October, 1969.

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‡Formerly Instructor, University of Minnesota, Department of Pathology and Veterans Administration Hospital, Minneapolis.



Fig. 1—Roentgenogram of a typical honeycombed lung representing a case of muscular cirrhosis of the lung.

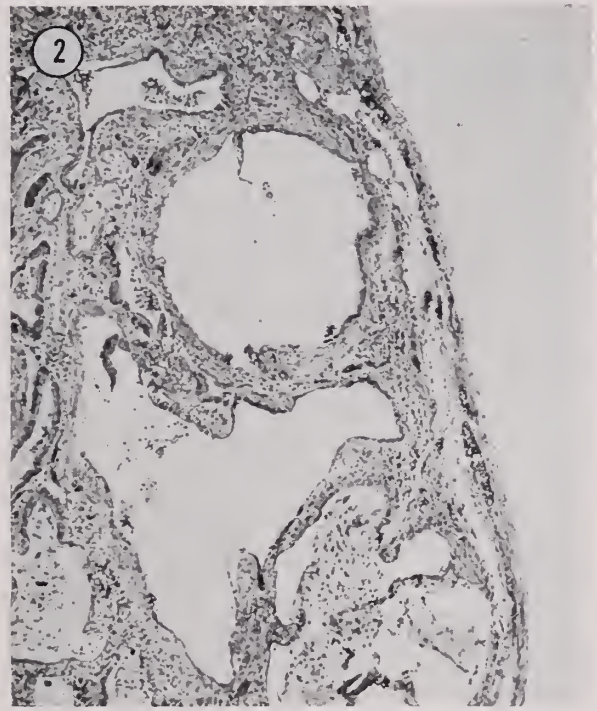


Fig. 2—Microphotogram of the same lung showing diffuse brochiolectasis.

Desquamative Interstitial Pneumonia

In 1965 a new entity was described by Liebow et al.,[19] termed desquamative interstitial pneumonia. This disease was said to behave clinically much like the nonfatal form of the Hamman-Rich type of interstitial pulmonary fibrosis. The patients had a similar progressive respiratory distress and impaired gas diffusion capacity.

Desquamated Cells

Histopathologically desquamative interstitial pneumonia is characterized by massively desquamated cells in the alveolar spaces.

These cells contain granules which stain intensively purple when using the periodic acid-Schiff method. Liebow considers them to be the large alveolar cells or septal cells which he termed granular pneumocytes. Unlike what was found in the Hamman-Rich type of interstitial fibrosis, no hyaline membrane formation or necrosis was observed.

Proliferation of Lymphocytes and Reticulin

Accumulation of lymphocytes which sometimes formed follicles was also seen. Similar to the Hamman-Rich type of interstitial fibrosis, there is also proliferation of reticulin fibers (Figure 5). Liebow's cases had no advanced

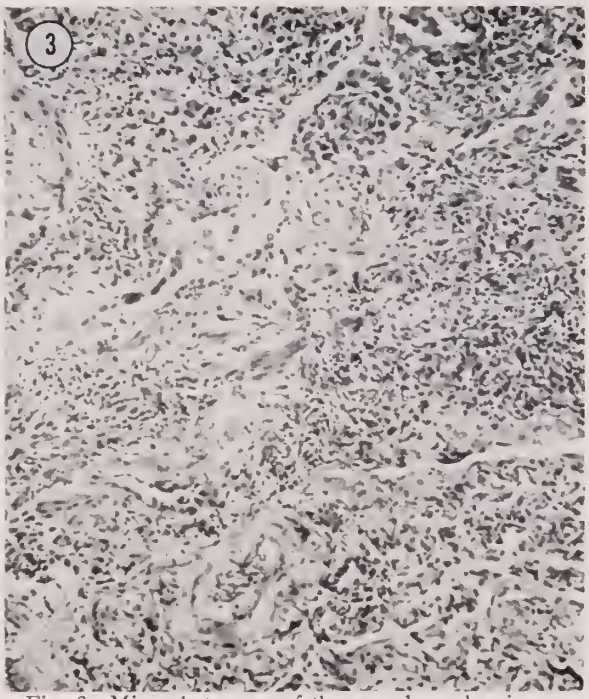


Fig. 3—Microphotogram of the same lung showing proliferation of smooth muscle fibers.



Fig. 4—Lung specimen of a case with muscular cirrhosis of the lung showing a nodular surface resembling the liver in Laennec's cirrhosis. The broken bulla in the upper portion is an incidental occurrence.

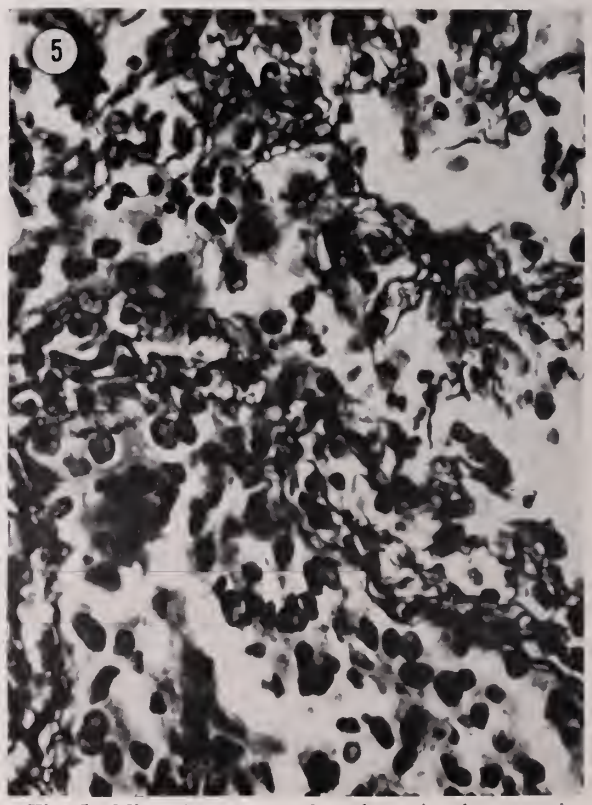


Fig. 5—Microphotogram of a lung in desquamative interstitial pneumonia showing reticulin proliferation through the use of silver staining.

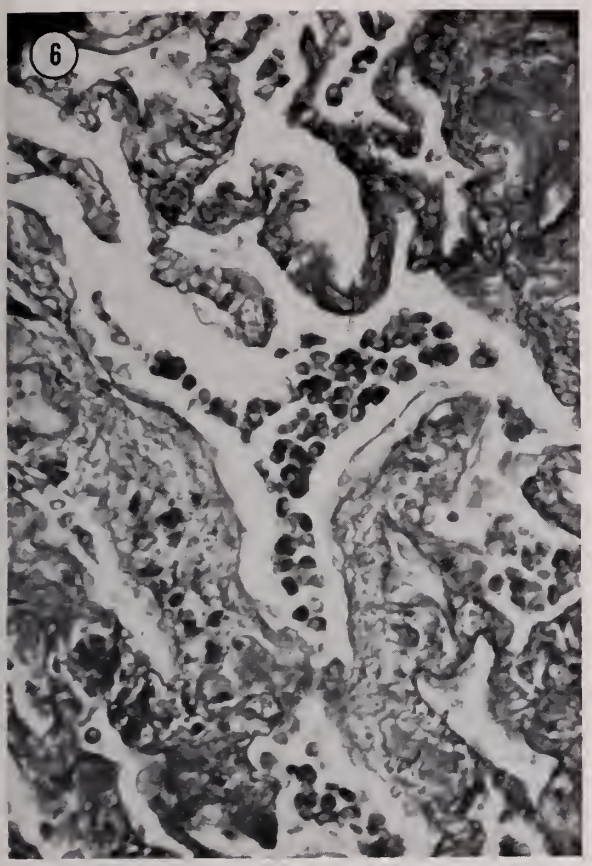


Fig. 6—Microphotogram of a lung section showing desquamated cells in the air spaces stained deep purple with periodic acid-Schiff method.

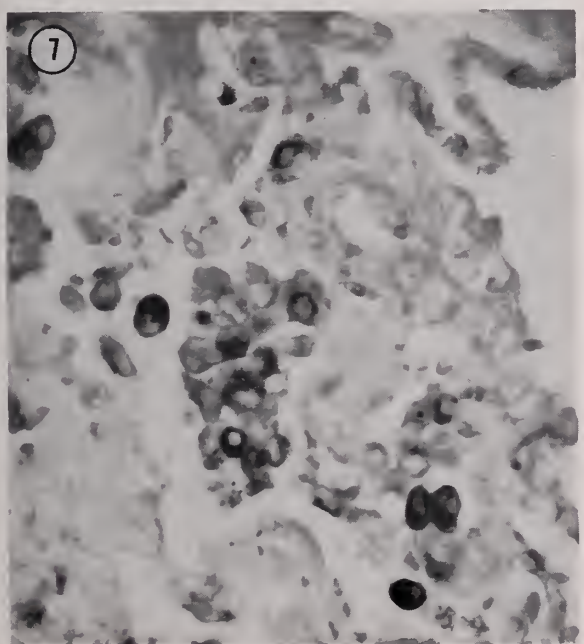


Fig. 7—The same cells as in Figure 6 also did stain strongly positive for iron.

forms, but in a subsequent series[7] there were patients with 10 years of follow-up who had undergone considerable thickening of the interalveolar septa. One patient in this series had developed honeycombing.

Observations of Our Study

Following these reports we compared roentgenographic appearances with histopathological findings in our old and new cases of interstitial fibrosis to find a way of distinguishing between these two forms.

Muscular Cirrhosis of the Lung

As a result it became evident to us that both desquamative interstitial pneumonia and the Hamman-Rich type of pulmonary fibrosis can advance into the final honeycombed form with diffuse bronchiolectasis and smooth muscle hyperplasia: muscular cirrhosis of the lung.[16]

Positive Stain for Iron

We also found[16] that the desquamated cells in the air spaces stained strongly positive not only when using the periodic acid-Schiff method (Figure 6), but also for iron (Figure 7). According to Liebow's description, however, the *granular pneumocytes* do not stain blue for iron, and only occasionally is there a pale but diffuse staining. In contrast to this, the *pulmo-*



Fig. 8—Roentgenogram of a chest showing a grossly reticulated pattern due to diffuse interstitial fibrosis in a patient with concomitant mitral stenosis.

nary macrophages were described as often showing iron-positive granules. In the literature, case reports of desquamative interstitial pneumonia also appeared in which the granular pneumocytes had shown iron reaction.[9,22,14] The existence of such an apparent dual staining property in the desquamated cells caused us to speculate that granular pneumocytes which are characteristically iron-free and pulmonary macrophages which often contain hemosiderin may not differ basically as much as generally thought.

Phagocytic Activity

According to Bertalanffy,[1] *alveolar septal cells,* which are Liebow's granular pneumocytes, and the *pulmonary macrophages* are both believed to be of mesodermal origin, and both are capable of phagocytic activity. Moore and Shoenberg,[21] and later Deodhar and Bhagwat,[4] produced a desquamative interstitial pneumonia-like syndrome in rabbits by injecting intravenously Freund-Adjuvant, a mycobacterial water-in-oil emulsion. The accumulated intra-alveolar cells appeared to them to derive from the interstitial macrophages. Shortland et al.,[27] using light and electron-microscopy on their two cases of desquamative interstitial pneumonia, reported that the desquamated cells were not all granular pneumocytes. Although in one case they made up 90% of the cells, in the other they amounted to only 40%, while the remaining 60% were pulmonary macrophages.

Autopsy Material

When reviewing our autopsy material, we were fortunate to find a case of severe diffuse interstitial pulmonary fibrosis, which also had a concomitant valvular mitral stenosis of rheumatic origin.[16] The chest roentgenogram (Figure 8) taken after mitral commissurotomy showed a typical mitral heart with congestion of the pulmonary veins.

Interstitial Fibrosis

A heavily reticulated pattern due to interstitial fibrosis, however, was also noted. The microscopic slide (Figure 9) showed markedly thickened alveolar septa with collagen proliferation and massive desquamation of cells in the air spaces. Accumulation of lymphocytes typical of desquamative interstitial pneumonia was also noted.

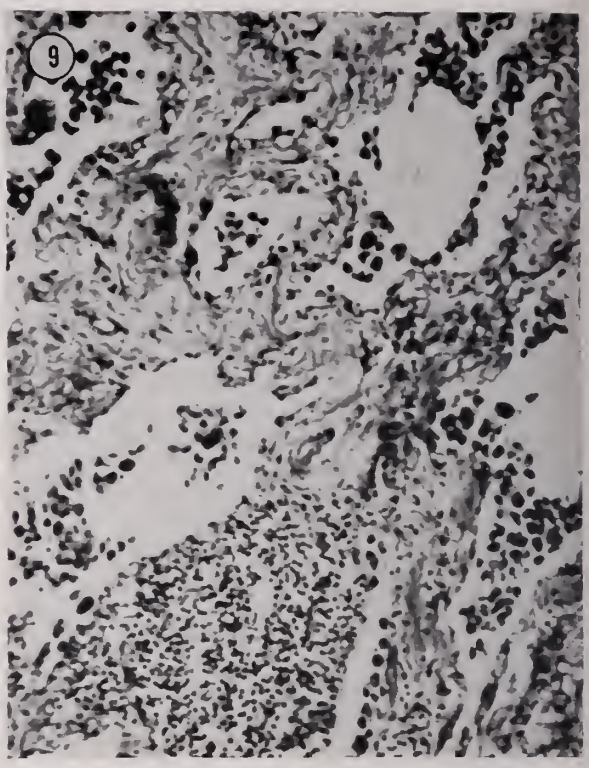


Fig. 9—Microphotogram of the lung in Figure 8 with periodic acid-Schiff-positive desquamated cells. Accumulation of lymphocytes is seen at viewer's left.

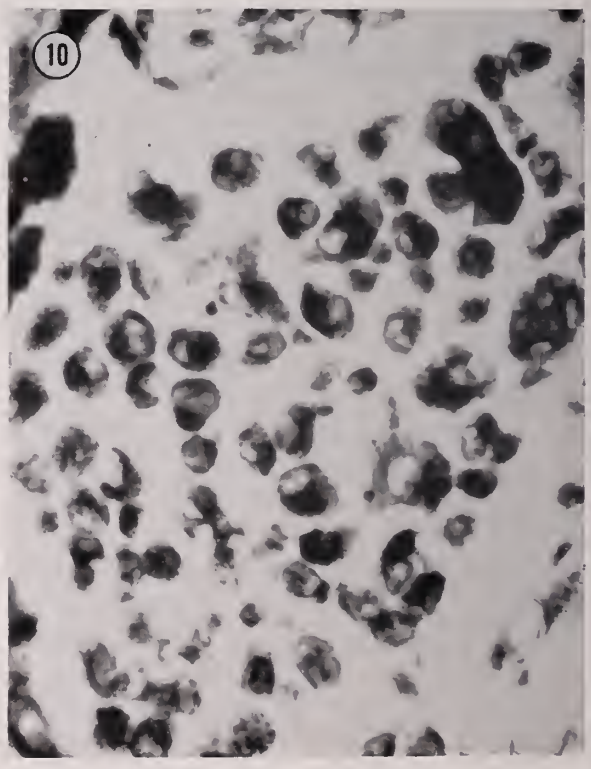


Fig. 10—Microphotogram of the lung in Figure 9 under higher magnification. The black areas in the cells represent the periodic acid-Schiff positively stained granules.

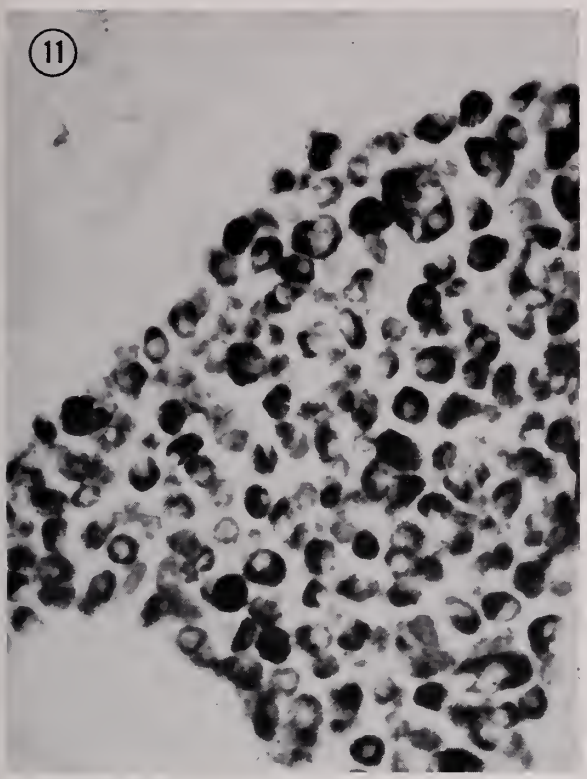


Fig. 11—The same lung section as in Figure 10, but stained for iron.

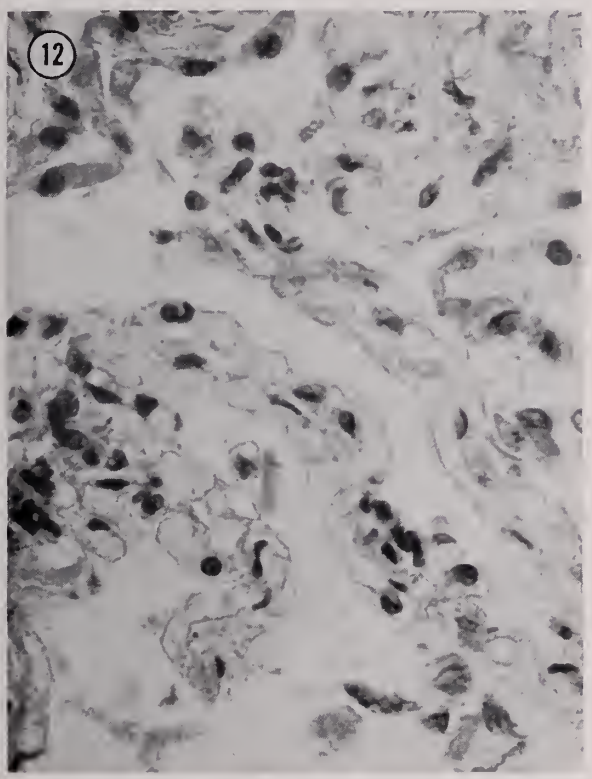


Fig. 12—Microphotogram of a lung in an early phase of fibrosing alveolitis showing swelling of the interalveolar septa.

Double Staining Properties

These desquamated cells stained purple due to periodic acid-Schiff-positive granules (Figure 10), but they also stained intensely blue for iron content (Figure 11). Some of these cells were fused to form multinuclear cells as described in the classical desquamative interstitial pneumonia. This case demonstrated very clearly that the same periodic acid-Schiff-positive granules can be definitely stained intensely blue for iron in a diffuse as well as in a granular pattern. This proved to us that *the difference between granular pneumocytes and pulmonary macrophages is not basic,* but that there is probably a transformation between them depending on the body's functional needs. In pulmonary congestion which may occur in any chronic pulmonary disease with cor pulmonale the granular pneumocytes appear to be able to phagocytize the decayed red cell material just as well as the pulmonary macrophages do. The same double staining property is found in the irradiated lung.

Two Similar Disease Processes

Both desquamative interstitial pneumonia and the Hamman-Rich type of interstitial fibrosis are without known etiology but appear to represent a hypersensitivity reaction which starts in the alveolar walls, a process termed "fibrosing alveolitis."[25,26] In the early phase there is swelling of the interalveolar septa (Figure 12) with proliferation of reticulin and desquamation of cells into the alveolar spaces. The chest roentgenogram initially is normal, but with progression of these changes, a stippled, ground-glass appearance develops. The next phase has a more reticulated appearance.

Desquamative Interstitial Pneumonia

In desquamative interstitial pneumonia, classically there is a triangular-shaped shadow radiating from the hilar regions down to the lung bases as described by Liebow and observed in Gaensler's series. The costophrenic angles are typically spared.

In one of our desquamative interstitial pneumonia cases verified by Dr. Liebow, the chest roentgenograms did not show such a triangular shadow but rather a generalized reticular pattern. The more advanced cases of desquama-

tive interstitial pneumonia show a gross reticulated appearance (Figure 13) while the most advanced cases show frank honeycombing (Figure 14).

Fibrosing Alveolitis

The gross specimens in that case have the typical nodular-cirrhotic appearance. Desquamated periodic acid-Schiff-positive cells are found in the air spaces, and in some cases lymphocytic infiltrates are seen not only in the lung but also in the liver. This indicates that the entity of fibrosing alveolitis is only part of a generalized hypersensitivity response of the body to an unidentified agent or possibly several agents.



Fig. 13—Grossly reticulated appearance of the lung roentgenogram in a moderately advanced case of fibrosing alveolitis.

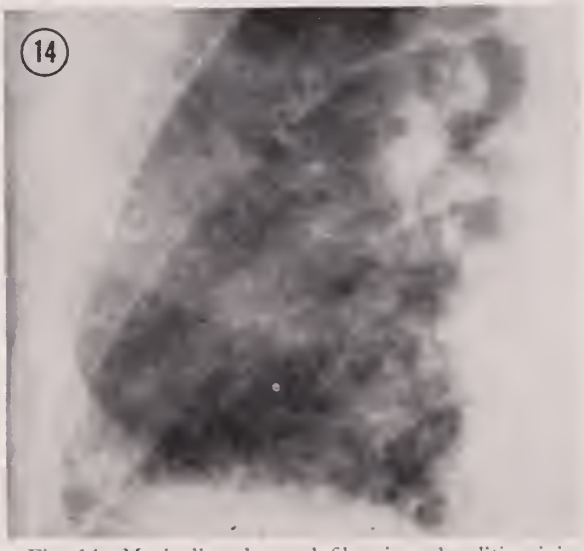


Fig. 14—Markedly advanced fibrosing alveolitis giving a honeycombed-lung appearance.

Mediastinal widening is rare in these two types of fibrosing alveolitis and, when present, an associated malignancy should be suspected. A bilateral hilar adenopathy in the honeycombed lung favors sarcoidosis or pneumoconiosis. Pneumothorax is known to occur in both types of fibrosing alveolitis but is most frequently seen in those honeycombed lungs caused by histiocytosis X. In the advanced stage called muscular cirrhosis of the lung, the inter-alveolar proliferating reticulin collagenizes and hyalinizes, causing progressive impediment of gas exchange. Hyperplasia of smooth muscle is a nonspecific body reaction.[18] The honeycombed appearance is produced by bronchiolectatic dilatation. Some believe this to be the result of bronchiolar dilatory compensation to the collapsed lung parenchyma,[13] while others believe it to be aided by partial obstruction of small bronchioles, producing a valve mechanism.[10]

Honeycombed lung is found in many of the auto-immune diseases such as scleroderma, dermatomyositis and rheumatoid arthritis, and also in tuberosclerosis and pulmonary hypersensitivity diseases such as farmer's lung. Fibrosing alveolitis also occurs in rheumatoid arthritis (Figure 15) and is undistinguishable from the chronic form of the Hamman-Rich type of in-



Fig. 15—Roentgenogram of a rheumatoid lung showing a grossly reticulated pattern.

terstitial fibrosis unless the joints are involved or rheumatoid factors are found in the serum.[20] Periodic acid-Schiff-positive desquamated cells are found in the air spaces.

Conclusion

In summary one can state that muscular cirrhosis of the lung represents the final stage of lung diseases caused by hypersensitivity reaction which predominantly affects the alveolar walls and can be called fibrosing alveolitis. The Hamman-Rich type of fibrosing alveolitis as well as Liebow's desquamative type of alveolitis (desquamative interstitial pneumonia) can progress into such a final form. Both types have overlapping features clinically, histopathologically, and roentgenographically. Positive iron staining of desquamated cells in the air spaces should not be used to rule out desquamative interstitial pneumonia, especially in the more advanced forms.

The radiologist who is aware of different diseases which produce honeycombed lung can make use of additional roentgenography as an aid in reaching the correct diagnosis. He can take roentgenograms of hands in suspected rheumatoid lung, perform gastrointestinal studies in suspected scleroderma, order skull views for suspected tuberosclerosis, and can greatly help the clinician to arrive at the correct diagnosis concerning a honeycombed lung.

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In the composure of a salad every plant should bear its part like notes in music.
—John Evelyn.

Bruce on the Trail of the Tsetse

It was hot. Their sweat dimmed the lenses of their microscopes; they rejoiced in necks cramped from hours of looking; they joked about their red-rimmed eyes. They gave strange nicknames to their sick cows and horses, they learned to talk some Zulu. It was as if there were no Director-General or superior officers in existence, and Bruce felt himself for the first time a free searcher.

And very soon they made their first step ahead; in the blood of one of their horses, sick to death, Bruce spied a violent unwonted dancing among the faintly yellow, piled-up blood corpuscles; he slid his slide along the stage of his microscope, till he came to an open space in the jungle of blood cells.

There, suddenly, popped into view the cause of the commotion—a curious little beast (much bigger than any ordinary microbe though), a creature with a blunt rear-end and a long slim lashing whip with which he seemed to explore in front of him. A creature shaped like a panatella cigar, only it was flexible, almost tying itself in knots sometimes, and it had a transparent graceful fin running the length of its body. Another of the beasts swam into the open space under the lens, and another. What extraordinary creatures! They didn't go stupidly along like common microbes—they acted like intelligent little dragons. Each one of them darted from one round red blood cell to another; he would worry at it, try to get inside it, tug at it and pull it, push it along ahead of him—then suddenly off he would go in a straight line and bury himself under a mass of the blood cells lining the shore of the open space.

"Trypanosomes—these are!" cried Bruce, and he hurried to show them to his wife. In all animals sick with nagana they found these finned beasts, in the blood they were, and in the fluid of their puffy eyelids, and in the strange yellowish jelly that replaced the fat under their skins. And never a one of them could Bruce find in healthy dogs and horses and cows. But as the sick cattle grew sicker, these vicious snakes swarmed more and more thickly in their blood, until, when the animals lay gasping, next to death, the microbes writhed in them in quivering masses, so that you could swear their blood was made of nothing else. . . . It was horrible!*

*Paul de Kruif: Microbe Hunters.

It's the Law

Physician Not Liable for Urinary Incontinence After Operation

A patient sued his physician for urinary incontinence following prostatic resection. Following the surgery, the patient was totally incontinent of urine.

The physician testified that the patient had been informed prior to surgery of the risk of incontinence even when due care was observed in performing the operation. The physician stated that he did not think that incontinency was likely, but he could not guarantee the results of the surgery. The physician in court stated that incontinency occurs in a small percentage of prostate removal cases no matter how carefully the operation is performed.

The jury returned an unanimous verdict in favor of the physician and dismissed the law suit.

Holland v. Spitalny, Super. Ct., San Francisco Co., Docket No. 55 1307 (Cal., Oct. 3, 1969). The Citation, Vol. 20. No. 5, December 15, 1969.

Changes in Serum Lipids

During Administration of an Oral Contraceptive

HERBERT W. JOHNSON, M.D.* and GERALD B. LEE, M.D.†

WHEN NEW DRUGS are introduced for clinical use, reports of untoward side effects often follow. In some instances new drugs produce more problems than the original disease itself. This may be true of the vascular and hyperlipemic complications of oral contraceptives; therefore, as much evidence as possible should be accumulated before a decision is made regarding the ultimate use of so widespread and popular a medication.

Premenopausal women are relatively immune to cardiac and cerebrovascular occlusive disease. The protective factor declines at menopause, and the incidence of occlusive vascular disease approaches that of the male.[1] Oral contraceptives appear to disturb this protective mechanism, with an increasing incidence of occlusive vascular phenomena.[2]

Elevated serum cholesterol and triglyceride levels carry with them an increased incidence of pathologic vascular manifestations. If a physician prescribes a drug that increases the serum lipids and thus potentially increases cardiovascular and cerebrovascular disease in his patient, he should be aware of the risks

Oral contraceptives mimic early pregnancy. Since pregnancy normally shows an elevated cholesterol, cholesterol esters and triglycerides, the search for etiologic factors had centered upon changes in the serum lipids and lipoproteins.

In original studies, Pincus[3] in 1965 and Brady[4] in 1966 found no change in serum cholesterol and low density lipoproteins in premenopausal women on contraceptive pills. All other studies since that time have shown elevation of either serum cholesterol or triglyceride, but the actual number of patients involved has been few.

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In 1966 Aurell[5] studied eight women on Anovlar for one year and Wynn et al.[6] observed 102 women for three months on six different contraceptive medications. Both described elevation of serum cholesterol and triglyceride, low density and very low density lipoproteins. In 1969 Wynn et al.[7] repeated a similar study and found elevation of the serum triglyceride and low density and very low density lipoproteins. The cholesterol elevations were not definite. Hazzard et al.[8] studied 10 women and found significant elevations in serum triglyceride.

Methods

A study was set up whereby 25 females in the 18 to 30 year age group, in good health and with normal menstrual histories from a private practice population, who denied ever taking contraceptive pills, participated in a 12-week study. Each subject was given a tablet containing norgestrel 0.5 mgm and ethinyl estradiol 0.05 mgm® daily on a three week on, one week off schedule. A 12-hour fasting blood specimen was drawn before commencing the study, and fasting specimens were obtained after two, four, and 12 weeks on the drug. The patient's diet remained unchanged throughout the experiment.

Cholesterol determinations were done by the auto-analyzer,[9] the automated method for triglyceride[10] and electrophoresis[11] for lipoprotein.

Results

Triglyceride

Significant elevation of the mean serum triglyceride was found in a study of 25 women maintained on an oral contraceptive for a period of three months.

In all but seven of the 25 subjects the serum triglyceride was elevated to greater than 50 per cent of the control value ($p > .001$) at one

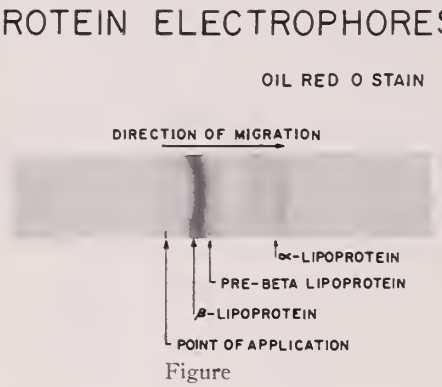
or more time intervals in the study. In these subjects the mean triglyceride value before starting the oral contraceptive was 72 mgm%. It rose as high as 220 mgm% in some subjects after 12 weeks on the drug. There were almost as many elevations of serum triglyceride after two weeks on the oral contraceptive as after 12 weeks on the drug.

Cholesterol

The mean serum cholesterol was not significantly elevated. In only three cases was there significant elevation of serum cholesterol.

Pre-Beta Lipoprotein

In seven subjects the vehicle for serum triglyceride, pre-beta lipoprotein, became distinct on lipoprotein electrophoresis. This is typified by one subject whose triglyceride rose from 99 mgm% to 223 mgm% and in which the distinct pre-beta lipoprotein band is shown in the Figure.



Figure

In seven cases the serum triglyceride remained relatively unchanged during the study.

Discussion

Significant elevations of triglyceride occurring within two weeks of the administration of contraceptive medications must be secondary to either increased mobilization or increased production of triglyceride or to decreased removal or utilization. Hazzard[8] was unable to conclude which of the above factors might be the major one involved. Administration of oral contraceptives was accompanied by (1) depression of the postheparin lipolytic activity causing a decrease in removal of triglyceride from the blood stream and (2) elevation of the basal immuno-reactive insulin levels which could result in increased hepatic triglyceride synthesis. Both of these factors may promote increased triglyceride levels but, as the author points out no definite conclusions could be drawn. Interestingly, diametrically opposite results were reported by Wynn et al.[7] who found no significant correlation between plasma insulin levels and changes in serum triglyceride.

The exact etiologic role of the two compounds that are combined in the oral contraceptive is also an undetermined factor. In general, the administration of synthetic estrogens has been shown to decrease serum low density lipoprotein, to increase serum high density lipoprotein, and to lower total serum cholesterol.[12,13] On the other hand, elevations of serum triglyceride have been reported following the administration of conjugated equine estrogens.[14] There has not been sufficient work done on the progestagens to draw any conclusions as yet. Whether the estrogenic and progestagen effects on serum lipids are modified in some way when the two agents are combined is also unknown. Thus, while the mechanism of elevation of serum triglyceride remains unknown, the fact that it does occur places a new responsibility upon the physician.

Summary

Serum cholesterol and triglyceride levels studied in a group of 25 young women before and during a 12-week interval on an oral contraceptive medication showed significant elevation ($p > .001$) of the serum triglyceride in 18 of the 25 women.

The serum cholesterol was elevated in only three of the 25 women. Protein electrophoresis showed a distinct pre-beta lipoprotein band in seven of the subjects.

If, as is becoming a more and more accepted thesis, elevation of serum lipids is intimately related to increased atherosclerosis, the long-term use of oral contraceptives may well produce a significant increase in cardiovascular and cerebrovascular disease in premenopausal women.

Acknowledgement

We wish to thank Dr. N. J. Lilliberg and Dr. J. R. Lees of St. Paul, Minn., for referral of the majority of patients in the study.

References may be secured from the author or the reprints.

And stay the bright hour ere it passeth away.—Culinary Almanac.

Joint Involvement following Vaccination for Rubella

An Unusual Presentation in an Adult

AMOS S. DEINARD, M.D.* and P. J. BILKA, M.D.†

Sir William Osler[1] first described arthritis as a complication of naturally-occurring rubella. Subsequent reports[2,3] have described this relationship more extensively. The usual situation, in post-pubertal females, has been that the arthritis occurred, typically in association with the rash, at the time of sero-conversion, lasted from two to 28 days, with a mean time of approximately one week, involved the proximal interphalangeal and metacarpophalangeal joints most often, was self-limited and was usually responsive to salicylates.

With the recent advent of rubella vaccine, cases are now being reported of post-vaccination arthritis in young adult women. For example, Gold et al.[4] reported that, in a group of 46 sero-negative adult women who had received the Cendehill strain of vaccine, four mild to moderate cases of arthralgia developed from eight to 28 days post vaccination and lasted from one to six days. Similar observations have been recorded in situations where other strains of rubella vaccine have been used.[5,6]

The following case is reported for three reasons: (1) the arthritis developed unusually late after the vaccination (30 days), (2) it persisted for an unusually long time (nine weeks) and (3) many joints were involved, some to a degree that suggested rheumatoid arthritis.

Case Report

The patient, a 27-year-old white female, was in good health prior to receiving an immunizing dose of rubella vaccine (Cendehill strain†). Together with her two children, she had participated in a field trial of the vaccine. Since she was found to be a sero-negative contact, she was immunized at the completion of the family study. Her children had no difficulty following vaccination. She experienced no physical discomfort for four weeks; however, from the 30th day onward she noted fatigue, periodic chills and painful stiff joints in the morning, improving as the day progressed. There was no history of an antecedent sore throat; she was not taking oral contraceptives or other drugs; there was never any skin rash or fever. Ten grains of aspirin every four hours gave no relief. She was seen in clinic for the first time on the 35th day following vaccination.

Pertinent findings on physical examination were limited to the joints. There was neck pain, following right lateral flexion, as well as distinct temporomandibular joint pain. Both wrist joints were tender and had a spongy feel; they were painful on dorsiflexion or palmar flexion. The elbows were slightly tender, as were the left proximal interphalangeal joints of the fourth and fifth fingers, the left fourth and fifth metacarpophalangeal joints and the right third proximal interphalangeal joint. Both ankles were diffusely painful and stiff upon motion, while the right ankle was distinctly tender following direct pressure.

Initial laboratory data were as follows:

Antistreptolysin titer less than 100 Todd units; hemoglobin—12.8 gm %; white blood count—6,550 cells/mm.^{3}, with a normal differential; erythrocyte sedimentation rate —16 mm. at 60 minutes; two-hour LE clot test—negative; rheumatoid factor (latex fixation method)—1:1280.

This last test was repeated seven and 14 days after the first assay and was negative each time, suggesting that the original determination had been in error. Over the next nine weeks the white count and sedimentation rate were repeated on several occasions; the values were always within normal limits. Roentgenographic examination of the right wrist, elbow and shoulder and left ankle, one month after the first clinic visit, revealed no pathology.

During the two weeks following her first clinic visit, additional small joints became involved. Many of them showed distinct synovial tenderness without any definite thickening except, perhaps, over the lateral aspect of the left ankle and over a few of the left metatarsal joints. Four weeks following the onset of symptoms, the previously involved joints were still tender. However, there was no evidence of effusion or synovial thickening. Six weeks after the onset of symptoms, most of the joints were still minimally tender. The right ankle and several

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†Marketed by Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.

of the right metatarsals remained painful but free of synovial thickening. The continued absence of definite thickening ultimately precluded a diagnosis of rheumatoid arthritis. Not until nine weeks following the onset of symptoms did the joint discomfort diminish so that the patient could resume normal activity without any medication. Since that time she has been in good health, with no further joint involvement.

When first seen, she was started on salicylate therapy and bedrest. Following the second clinic visit the salicylate dosage was increased because of increasing joint involvement. Ultimately, 100 grains per day were required to eliminate joint discomfort.

Since her initial titer against the rubella virus, drawn at the beginning of the family study, was less than 1:8, as measured by the hemagglutination-inhibition method, she was considered to be sero-negative. At the completion of the family study, her serum was retested; again, there was a titer of less than 1:8. Approximately three weeks after the onset of symptoms, a repeat serum analysis was performed by the laboratory of Smith, Kline and French. At that time her serum had a titer of 1:64.

Discussion

We are publishing this case to emphasize a complication of rubella vaccination in a young adult female. Although it was initially thought to occur infrequently, it is being reported with increasing frequency since the release of rubella vaccine. Rubella arthritis has been mistaken for rheumatoid arthritis and other serious forms of joint disease. Thus it is important for the physician to be aware of this "new form" of arthritis.

Our case is of special interest because: (1) the symptoms were late in onset (30 days); (2) the symptoms persisted for a prolonged period (nine weeks); (3) most of the joints of the body were involved.

The literature has few descriptions of arthritis with the above-mentioned special features of this case. Cooper et al.[5] have described one case where arthralgia developed after the 30th day but lasted for only two days. In addition, the involved joints had been symptomatic two years before with "rheumatoid arthritis." Another of Cooper's cases had ten weeks of joint involvement; but her symptoms developed 17 days after vaccination and were limited to the left knee which had been symptomatic six years prior to vaccination, lasting at least four years and requiring medical consultation at that time. Our patient, on the contrary, had no prior history of joint involvement.

When our patient was first seen, the symptoms and physical findings suggested rheumatoid arthritis, a diagnosis which was strengthened by an initial titer for rheumatoid factor of 1:1280. However, this diagnosis was ultimately disproved by the finding, on subsequent assay for rheumatoid factor, of two consecutive negative results and by the repeated failure to demonstrate definite synovial thickening or joint effusion. The half-life of rheumatoid factor, an IgM molecule, is five days.[7] So, if the initial assay for rheumatoid factor had been correct, the first repeat value, done seven days later, should have been 1:640 rather than zero, while the second repeat study should have been 1:160. Hence the total picture was more compatible with a diagnosis of joint involvement secondary to vaccination with rubella vaccine. This case was treated successfully and conservatively with salicylates and a reduction in activity.

Acknowledgment

The authors wish to acknowledge the helpful advice of Dr. Arthur R. Page, Associate Professor, Department of Pediatrics, University of Minnesota Hospital, Minneapolis, Minnesota.

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Beef Broth	22	Vegetable	68
Consommé	29	Tomato	69
Chicken with Rice	43	Cream of Asparagus	70
Chicken Gumbo	48	Cream of Chicken	76
Chicken Noodle	54	Cream of Mushroom	115
Cream of Potato	58	Green Pea	116
Chicken Vegetable	60	Cream of Shrimp (Frozen)	132
Vegetable Beef	66	Bean with Bacon	133

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75 million more Americans—what impact on health care?

Because of a declining birthrate in the United States—attributable in no small measure to the widespread use of contraceptives—our population in thirty years is expected to be *only* 280 million, while the world population is expected to double, reaching 7 billion.

But the word "only" has an ironic ring to ecologists who warn of cities resembling overcrowded, contaminated rat colonies, of respiratory and mental diseases reaching epidemic proportions and of a health-care community virtually overwhelmed by the burden.

The global consequences may be no less devastating. Ecologists estimate that every American has roughly fifty times the negative impact on the Earth's life-support systems of, say, a citizen of India. In these terms, adding 75 million Americans would be equivalent to adding 3.7 billion Indians to the world population.

**For the complete brochure, an others in the series as they appea please write to Searle or ask your Sear representative.* Explored in the fort coming issues will be the role of bir control on family pressures and i effects on the family; the influences poverty, ethnic factors and marit status; its role in illness, its genet implications and its effects on th emotional and behavioral life of th individual.

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Actions—Demulen acts to prevent ovulation by inhibiting the output of go-adotropins from the pituitary gland. Demulen depresses the output of both he follicle-stimulating hormone (FHS) and the luteinizing hormone (LH).

Special note: Oral contraceptives have been marketed in the United States nce 1960. Reported pregnancy rates vary from product to product. The ef-ectiveness of the sequential products appears to be somewhat lower than that f the combination products. Both types provide almost completely effective ontraception.

An increased risk of thromboembolic disease associated with the use of ormonal contraceptives has now been shown in studies conducted in both reat Britain and the United States. Other risks, such as those of elevated lood pressure, liver disease and reduced tolerance to carbohydrates, have ot been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in sub-rimate animal species in multiples of the human dose increases the frequency f some animal carcinomas. These data cannot be transposed directly to man. he possible carcinogenicity due to the estrogens can be neither affirmed nor efuted at this time. Close clinical surveillance of all women taking oral con-raceptives must be continued.

Indication—Demulen is indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disor-ders, cerebral apoplexy or a past history of these conditions, markedly im-paired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of hrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary mbolism and retinal thrombosis). Should any of these occur or be suspected he drug should be discontinued immediately.

Retrospective studies of morbidity and mortality conducted in Great Britain nd studies of morbidity in the United States have shown a statistically sig-ificant association between thrombophlebitis, pulmonary embolism, and erebral thrombosis and embolism and the use of oral contraceptives. There ave been three principal studies in Britain [1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in he study by Vessey and Doll[3] was about sevenfold, while Sartwell and asso-iates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident ause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to valuate a difference between products. However, the study suggested that here might be an increased risk of thromboembolic disease in users of se-uential products. This risk cannot be quantitated, and further studies to con-irm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medi-cation should be withdrawn.

Since the safety of Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. f the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been dentified in the milk of mothers receiving these drugs. The long-range effect o the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Demulen. Therefore, if such tests are abnormal in a patient taking Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Demulen may mask the onset of the climacteric. The pathologist should be advised of Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted; anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

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Editorials

148 Femoral Shaft Fractures in 144 Patients*

Intramedullary fixation of the fracture of the femur has given us thirty years of experience with increasing popularity. With improved surgical techniques, instrumentation and better understanding of the clinical indications and its limitations, intramedullary nailing offers greater advantages over conservative treatment of skeletal traction. It allows rigid fixation, early ambulation, early motion of hip and knee joint, a shorter hospital stay and consequently a *much reduced hospital cost.* The analysis of Sletten et al. supports these conclusions. Many complications of intramedullary nailing, particularly infection, can be avoided or reduced to a minimum by good preoperative and postoperative hospital care, good surgical technique, and most of all better selection of patients. Delayed intramedullary nailing of open fractures for 10 to 14 days after the wound is healed, diminishes the incidence of infection. Thromboembolic phenomena, bed sores, pneumonia and non-union in the nailed femur are infrequent in operated patients.

Skeletal traction in the treatment of femoral shaft fractures is a safe method but a difficult one. One aligns the fracture in satisfactory position in 48 to 72 hours without distraction. It requires serial x-rays to avoid malalignment, malunion, excessive shortening and distraction. In other words, it requires meticulous and careful daily observation and adjustment of the traction for a long period of time. As a result of prolonged traction for eight to 12 weeks, varying degrees of knee joint stiffness are a common sequela of traction treatment.

Ergo, the treatment of femoral shaft fracture, if the requirements are met, is intramedullary nailing in the hands of an experienced surgeon.

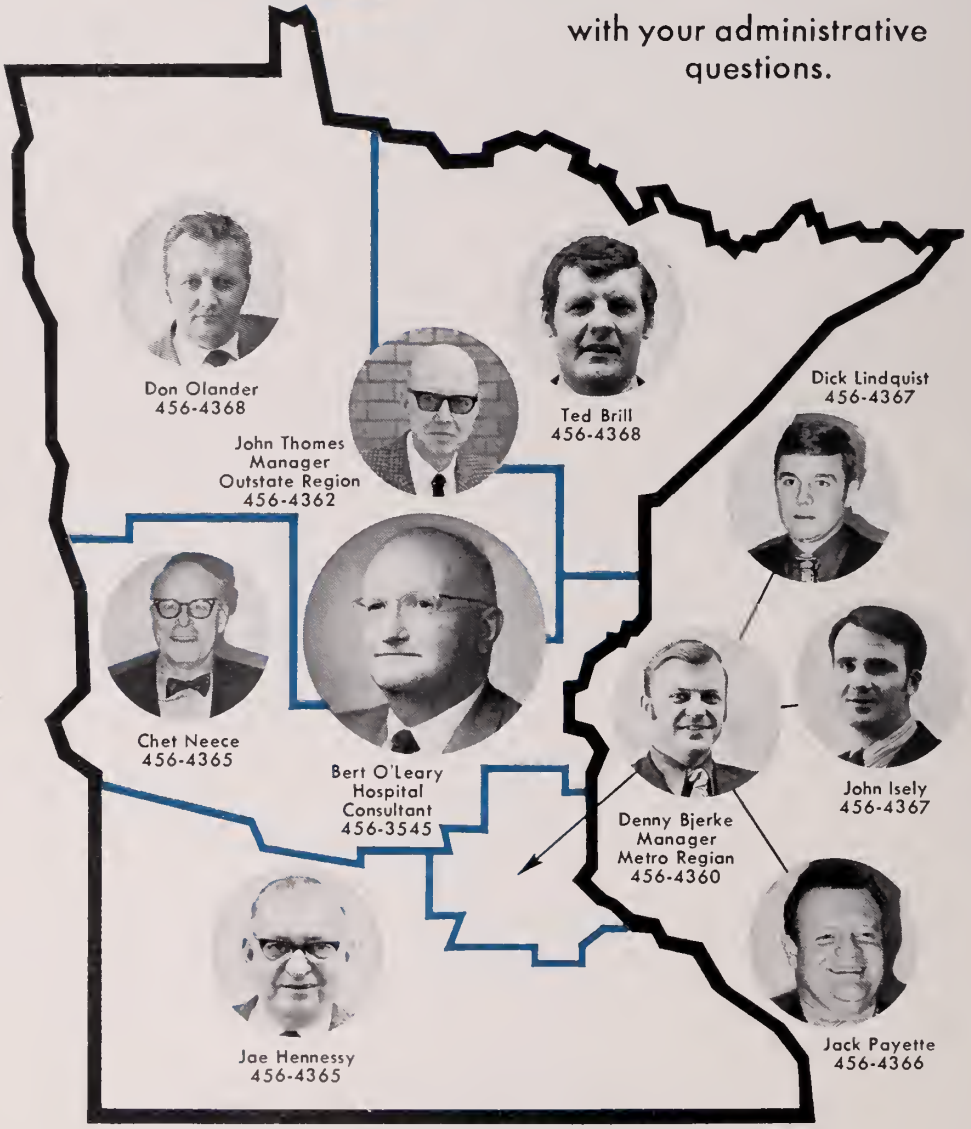
Ramon B. Gustilo, M.D.
Minneapolis, Minnesota

*Sletten, Richard et al.: 148 Femoral Shaft Fractures in 144 Patients. Minnesota Med 54:261, 1971.

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Editor's Soliloquy

Us Gents

With the advent of spring—that resurrective season of blooming crocuses at the margins of melting snowdrifts, the first sturdy robin listening out an unwary angleworm, the invisible chattering grosbeaks busily building their nests before introducing themselves to the feeder, and the first golfer skirting the spongy, forbidden greens—we are again honoring our Fifty-Club members: those gentlemen of rare wisdom: a distinguishing asset generally belied by the deceptive tranquility of their demeanor.

True, these eminent seniors are being superseded and perhaps superannuated by a younger, vociferous group of hot-bloods: hirsutely adorned individuals with visionary and hence unvindicated ideals; out to conquer the world by turning it inside out and upside down to shake it free of what they regard as a hoary mould of ancient, dusty cobwebs, so that fresh air and sunlight can permeate and sterilize it.

Your Fifty-Club members are experientially well-qualified but hesitant to proffer unasked advice, for too often their valuable counsel is ignored, occasionally even scorned. So, regretfully, they accept the dictum that most of history is about to be repeated because it will not be listened to.* These gentlemen have endured, if not willingly tolerated, most of the socio-political-economic evils that have perennially corrupted their social milieu; and they have neither taste nor inclination for perpetuating them. Besides, they have seen other dichotomies in life than the generation gap. Perhaps to them dichotomies represent nothing more than the inevitable swing of the proverbial pendulum, without which the clock would stop! Furthermore, because the terminal pages in life's book are almost all turned over for them, these men are content to be tender with the last few leaves, lest they be brittle and crumble in the process like the pages of an ancient heirloom volume that the inexorable hand of Time has weathered, too fragile for rough handling.

I was about to examine a litigant who claimed that his aching joints, his failing vision, his impaired hearing, and his wobbly knees were all ascribable to a minor accident in which he had bruised his thumb. As a preliminary to the major examination which was to follow, we, in our mutual seniority, eyed each other, he through his high-diopter post-cataract lenses, and I through my trifocals. I hadn't yet noted his chronologic age of 72 as recorded by my office nurse, but mentally speculated that he might be 90. However, as our reciprocally appraising glances met I perceived a shrewd twinkle in his eye; and I had to respect the accuracy of his evaluation, while abnegating my own, as he sagely observed: "Us gents ain't getting any younger, is we?"

*Santayana: "Those who fail to listen to history are bound to repeat it."

Carl O. Rice, M.D.
Editor-in-Chief

OLD DOC HESS SAYS: Quit trying to improve your neighbor, try improving yourself.—C.O.R.

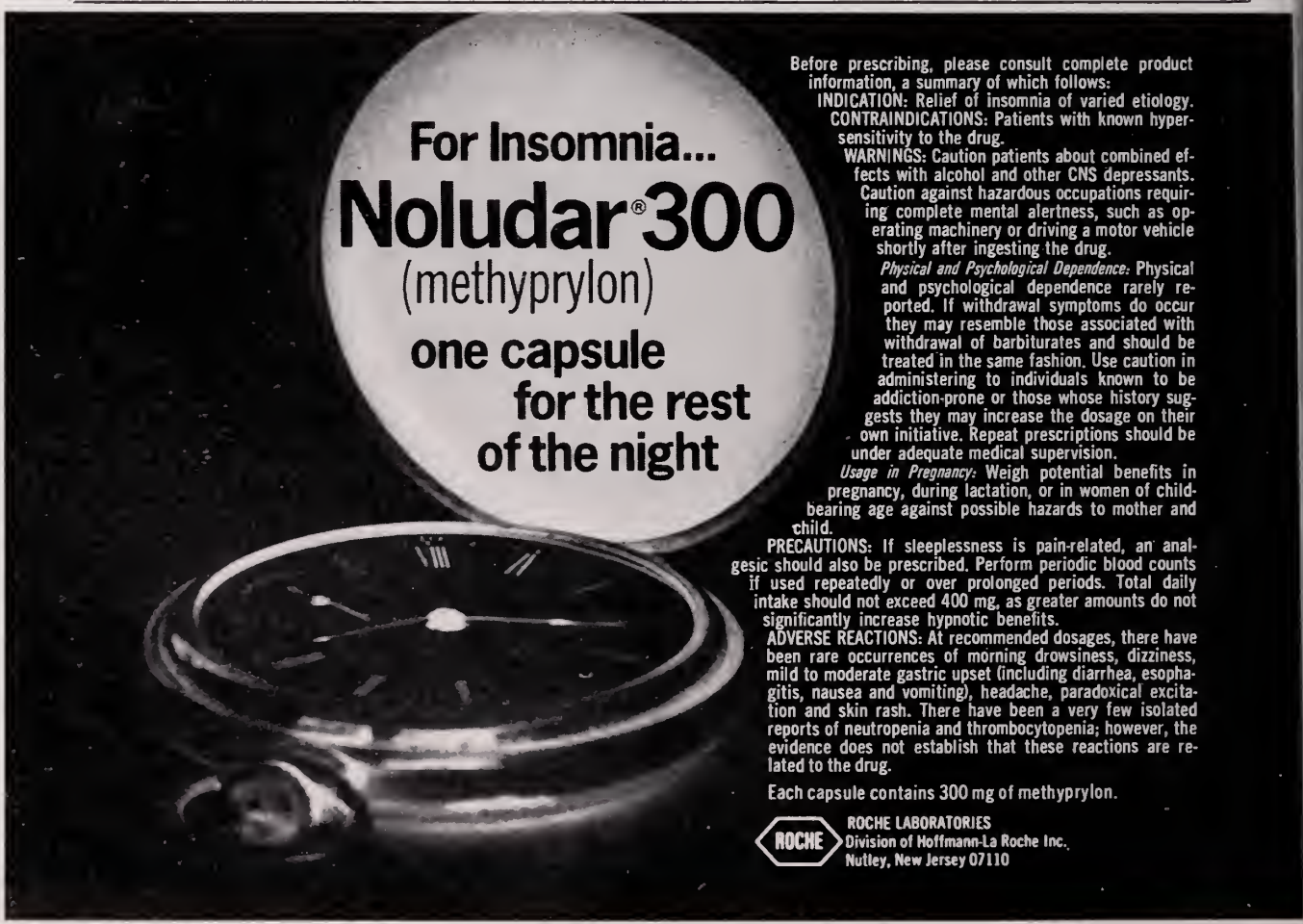




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Physical and Psychological Dependence: Physical and psychological dependence rarely reported. If withdrawal symptoms do occur they may resemble those associated with withdrawal of barbiturates and should be treated in the same fashion. Use caution in administering to individuals known to be addiction-prone or those whose history suggests they may increase the dosage on their own initiative. Repeat prescriptions should be under adequate medical supervision.

Usage in Pregnancy: Weigh potential benefits in pregnancy, during lactation, or in women of childbearing age against possible hazards to mother and child.

PRECAUTIONS: If sleeplessness is pain-related, an analgesic should also be prescribed. Perform periodic blood counts if used repeatedly or over prolonged periods. Total daily intake should not exceed 400 mg, as greater amounts do not significantly increase hypnotic benefits.

ADVERSE REACTIONS: At recommended dosages, there have been rare occurrences of morning drowsiness, dizziness, mild to moderate gastric upset (including diarrhea, esophagitis, nausea and vomiting), headache, paradoxical excitation and skin rash. There have been a very few isolated reports of neutropenia and thrombocytopenia; however, the evidence does not establish that these reactions are related to the drug.

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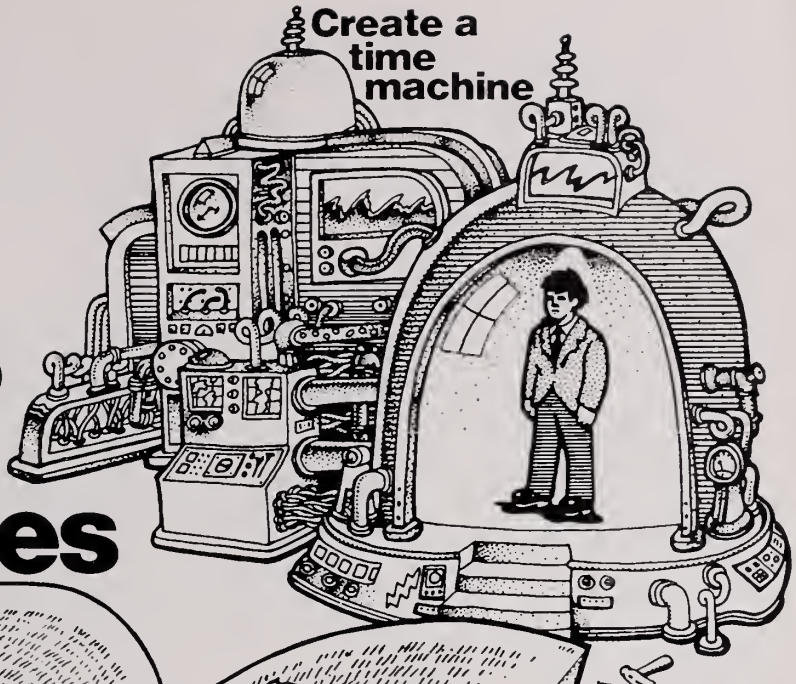
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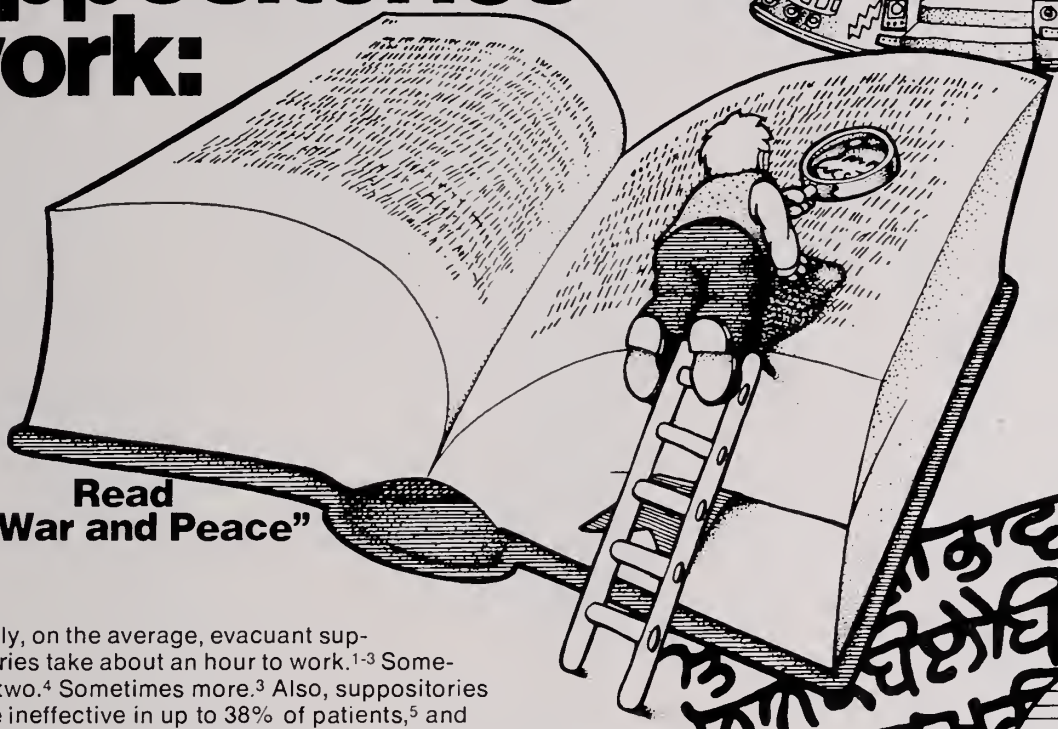


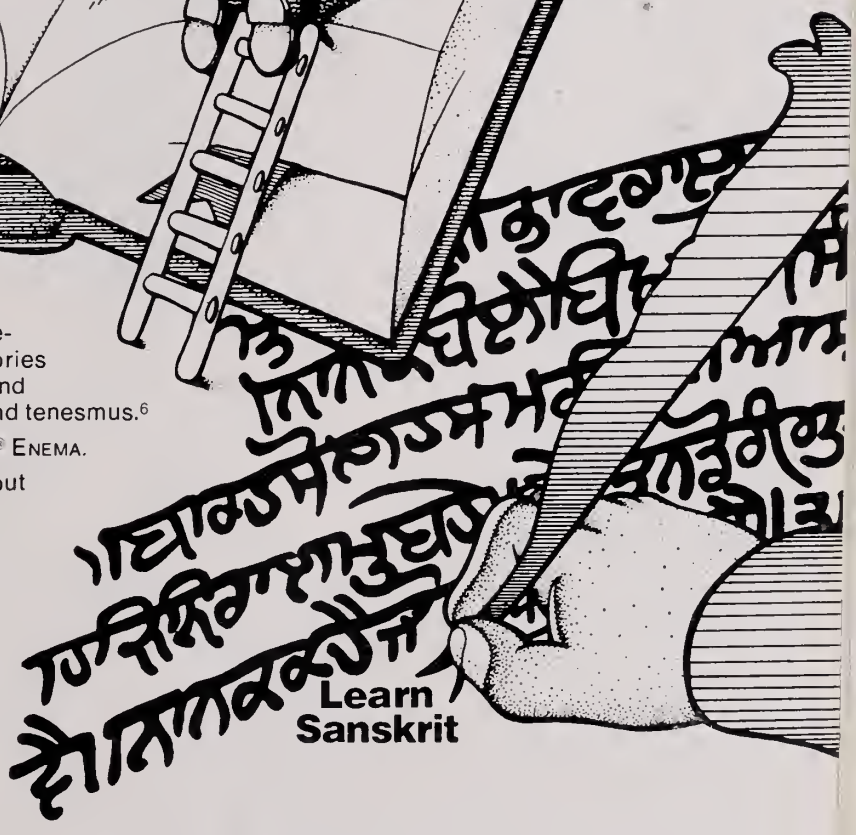
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References: 1. Blumberg, N.: Med Times 91:45, Jan., 1963. 2. Sweeney, W. J., III: Amer J Obstet Gynec 85:908, Apr. 1, 1963. 3. Weinsaft, P.: J Amer Geriat Soc 12:295, Mar., 1964. 4. Baydoun, A. B.: Amer J Obstet Gynec 85:905, Apr. 1, 1963. 5. Feder, I. A., Flores, A. and Weiss, J.: Amer J Gastroent 33:366, Mar., 1960. 6. Smith, J. J and Schwartz, E. D.: Western J Surg 72:177, May-June, 1964.

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*Slanger, A.: Med. Times *94*:150 (Feb.) 1966.

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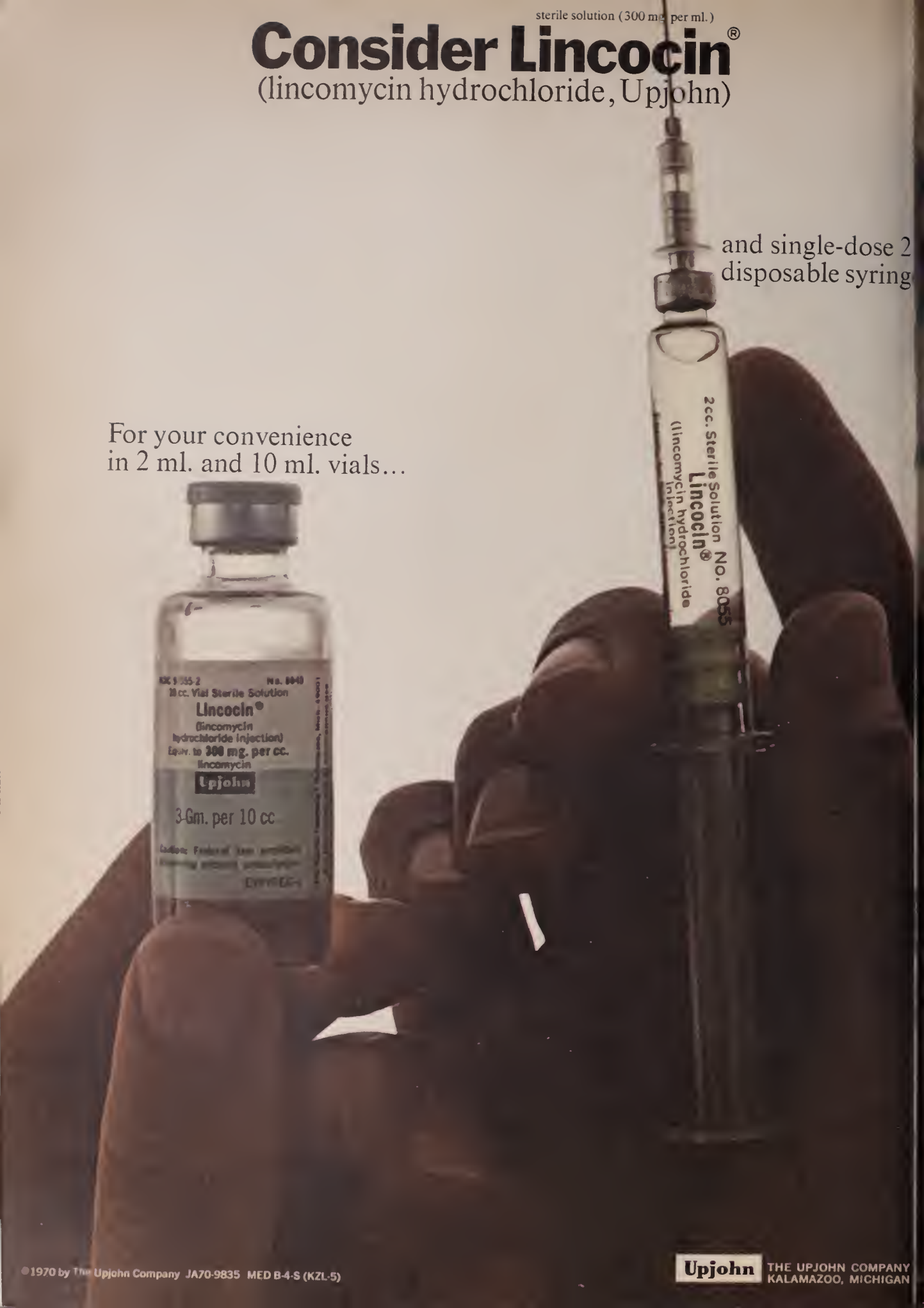
sterile solution (300 mg. per ml.)

Consider Lincocin®

(lincomycin hydrochloride, Upjohn)

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disposable syring

For your convenience
in 2 ml. and 10 ml. vials...



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A nce-popular treatment for back pains
s to have the seventh son of a seventh son
nd or walk on the patient's back.





The pain of earache was allegedly relieved by holding a hot roasted onion to the ear.

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wear a snakeskin round one's head.



A realistic approach to pain relief



Empirin'®

Compound with Codeine Phosphate gr. 1/2 No. 3

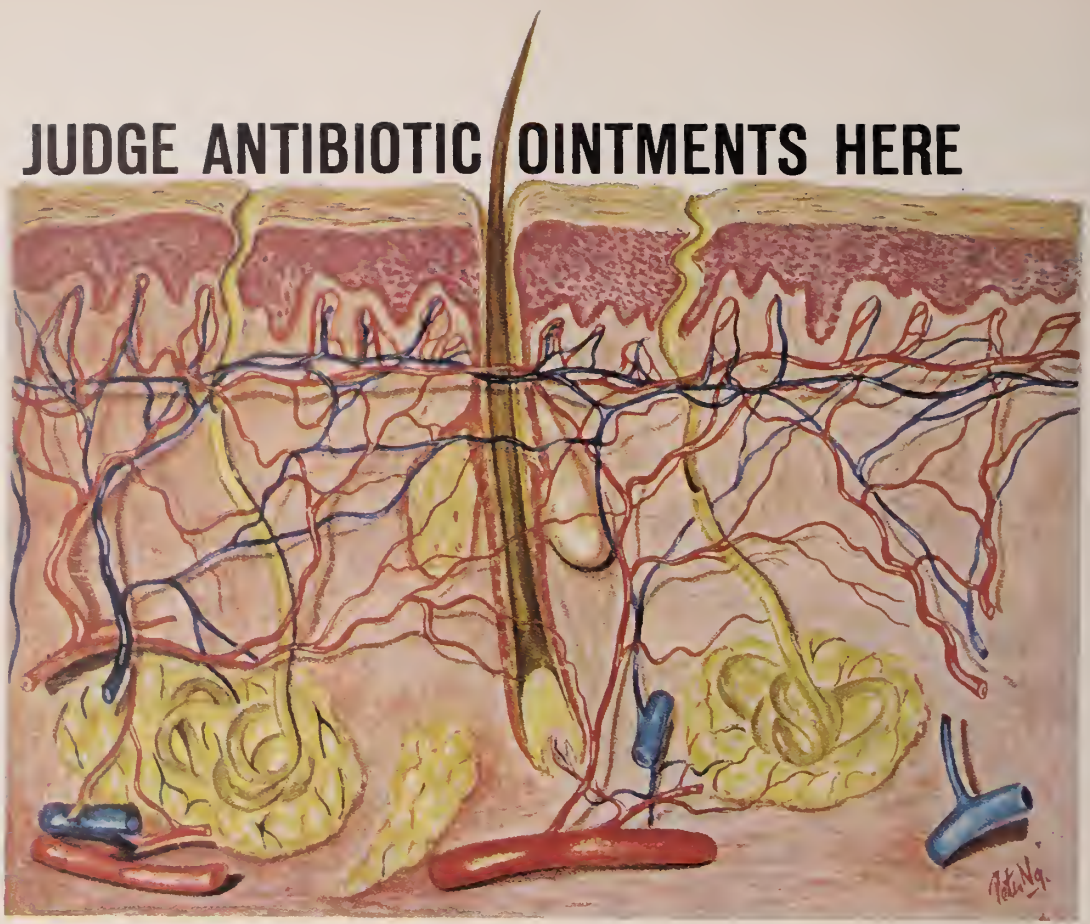
ach tablet contains:
odeine Phosphate gr. 1/2 (Warning—
ay be habit forming), Phenacetin gr. 2 1/2,
spirin gr. 3 1/2, Caffeine gr. 1/2.

keeps the promise of pain relief

W. & Co.' narcotic products are
ass "B", and as such are available on oral
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Tuckahoe, N.Y.

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Results on skin are final proof of any topical antibiotic's effectiveness

No in vitro test can duplicate a clinical situation on living skin. 'Neosporin' (polymyxin B—bacitracin—neomycin) Ointment has consistently proven its effectiveness in thousands of cases of bacterial skin infection. The spectra of the three antibiotics overlap in such a way as to provide bactericidal action against most pathogenic bacteria likely to be found topically. Diffusion of the antibiotics from the special petrolatum base is rapid since they are insoluble in the petrolatum, but readily soluble in tissue fluids. The Ointment is bland and nonirritating.

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Contraindications: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

Supplied: Tubes of 1 oz., ½ oz. with applicator tip, and ⅛ oz. with ophthalmic tip.

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Minnesota State Medical Association 118th Annual Meeting

Saint Paul, Minnesota

May 17, 18, 19, 1971

In the introductory pages of the Annual Meeting program mailed to all members of the Minnesota State Medical Association, President Raymond Jackman observed "I believe that the overall theme could best be described as 'innovations in the practice of medicine'."

The scientific program for the 118th Annual Meeting of the Minnesota State Medical Association will begin Monday, May 17, at 9:00 A.M. and will continue through Wednesday noon, May 19.

"In Depth" Scientific Sessions, Workshops and noon luncheons will focus on salient aspects of medical practice. The Committee has encouraged physicians to pre-register in order to save time, since those who do so will have their badges waiting for them when they arrive at the Advance Registration Desk in the St. Paul Hilton Hotel. The Committee emphasizes that attendance at the Workshop Sessions and the Alcoholism and Drug Abuse Forum is limited. Preregistration will help physicians to insure attendance at the Forum and Workshops of their choice.

For the convenience of physicians who wish to pre-register, advance registration materials have been enclosed with special mailings, monthly newspage mailings and the official Annual Meeting program.

The Scientific Program is approved for 13 prescribed hours by the American Academy of General Practice.

"It's all happening at the Hilton" because physicians can enjoy attendance of most annual meeting activities—all under one roof.

The 1971 hotel-based meeting represents an exciting new dimension for Minnesota physicians. The contemporary surroundings of the St. Paul Hilton will also provide an ideal setting for scientific and technical exhibits. The Committee on Scientific Assembly has indicated that the scientific exhibit entries for this meeting are particularly outstanding. The Committee also suggests that physicians visit the technical exhibits and express their appreciation to the business firms whose participation continues to insure the high quality of Association annual meetings.

Many of the more than fifty scientific and non-scientific committees have scheduled breakfast meetings in conjunction with the meeting, and physicians are urged to attend their respective committee meetings and participate in the business meetings and discussions as prescribed.

The calendar of meetings and special events is crowded with a variety of activities for physicians attending the meeting.

The Physician's Bridge Tournament, open to all physicians and their wives, will begin Sunday, May 16, at 7:30 P.M. in the Three Crowns (lobby level) of the Hilton Hotel. Duplicate bridge experience is not necessary, and there is no entry fee. Trophies will be given and advance registrations are requested.

The Dellwood Hills Country Club, White Bear Lake, will be the setting for the annual Physician's Golf Tournament. Tee off time is 10:00 A.M. Sunday, May 16; Greens Fee, $6.00. Golf tournament participants, their wives and all who attend the Annual Meeting are invited to attend a buffet dinner at the Dellwood Hills Country Club at 5:30 P.M. Ticket price is $6.00.

The Minnesota Heart Association will hold its Annual Meeting and Dinner, Tuesday, May 18, in the Hotel St. Paul.

The Minnesota Physiatric Society has scheduled a 6:30 P.M. dinner meeting Tuesday, May 18. The guest speaker will be Mr. C. Arthur Williams, Jr., Dean of the School of Business Administration, University of Minnesota. The dinner is open to all physicians. Contact Doctors Donald Erickson or Lloyd Wood at the Mayo Clinic, Rochester.

A dinner meeting will also be held by the Minnesota Chapter of the American Academy of Pediatrics, on Tuesday, May 18, at 6:30 P.M.

The St. Paul Regional Red Cross Blood Program will sponsor a 7:30 A.M. breakfast Wednesday, May 19, and will host physician representatives of hospitals served by the Red Cross Blood Program.

The Minnesota Chapter of the American College of Surgeons will hold its meeting Wednesday in conjunction with the Annual Meeting of the Association in the Hilton Pioneer Suite, and will begin with a 7:30 A.M. breakfast meeting of the Minnesota Committee on Trauma. The surgeon's luncheon will be held at 12:15 P.M. and will be followed by a 1:30 P.M. session on socio-economic and medico-legal considerations.

The Minnesota Academy of Ophthalmology and Otolaryngology will hold a dinner dance Tuesday, May 18, at 7:30 P.M., which will be preceded by a 6:30 P.M. social hour.

The Continental Ballroom of the St. Paul Hotel will be the setting for the Annual Banquet Monday, May 17, at 7:00 P.M. Fifty Club members will be honored guests. A 6:00 P.M. President's Reception will precede the banquet. Entertainment will be provided by the 3-M Musicmakers. There will be dancing following the banquet.

The Scientific program will begin Monday, May 17, at 9:00 A.M. in the St. Paul Hilton Hotel. A series of morning "In Depth" sessions will be held Monday through Wednesday. Six workshops have been arranged for Monday afternoon and three for Tuesday afternoon. Identical workshops will be held from 2:00 to 3:00 P.M. and 3:45 to 4:45 P.M. each day. The Committee recommends pre-registration for these workshops because of space limitations. Preference will be given to physicians who have pre-registered.

A timetable of Annual Meeting events follows, including a listing of workshop titles and scientific sessions. Physicians are urged to refer to this timetable or the official program which has previously been mailed to all Association members for additional Annual Meeting information.

The MSMA gratefully acknowledges the assistance of the following in contributing to the 1971 Scientific Program: Eli Lilly & Co., Intensive Coronary Care Unit Committee of the Minnesota Heart Association, Northlands Regional Medical Program, Minnesota Chapter of the American College of Surgeons, Committee on Medicine and Religion and the Subcommittee on Alcoholism and Drug Abuse.

SCIENTIFIC PROGRAM

St. Paul Hilton Hotel

MONDAY, MAY 17

9:00 A.M. to 10:00 A.M. ACUTE RESPIRATORY FAILURE
1) "Causes and Recognition"
M. B. Divertie, M.D., Rochester
2) "Management of the Airway and Control of Secretions"
E. P. Didier, M.D., Rochester
3) "Use of Oxygen and Assisted Ventilation"
Hugh D. Westgate, M.D., Minneapolis

10:00 A.M.—
10:30 A.M. INTERMISSION
Visit Scientific and Technical Exhibits

10:30 A.M.—
12:00 Noon ANTIBIOTICS
1) "Antibiotic Combinations and Gram-Negative Infections"
Wallace E. Herrell, M.D., Editor, Clinical Medicine, Northfield, Illinois
2) "Antibiotic Treatment of Gram-Negative Bacteremias"
Paul E. Hermans, M.D., Rochester
3) "Shock Associated with Gram-Negative Bacteremias"
Wendell Hall, M.D., Minneapolis

12:15 P.M. LUNCHEON
Dr. James F. Martin, Consulting Psychologist, Minneapolis "COMMUNICATION—WHO NEEDS IT?"

WORKSHOPS

2:00 P.M.—
3:00 P.M.. 1) "Consumptive Coagulopathy—The Intravascular Coagulation and Fibrinolysis (ICF) Syndrome"
F. J. Kazmier, M.D. and Paul Didisheim, M.D., Rochester

2) "Diagnosis of Thyroid Disorders"
Horace K. Ivy, M.D., Rochester

3) "Oral Hypoglycemic Agents"
Frederick C. Goetz, M.D., Minneapolis

4) "Gastrointestinal Bleeding"
Philip W. Brown, Jr., M.D., Donald C. McIlrath, M.D., Rochester

5) "The Dizzy Patient"
Frank M. Howard, Jr., M.D., Lawrence W. DeSanto, M.D., Rochester

6) "Aortic Aneurysms"
Philip J. Osmundson, M.D., James R. Pluth, M.D., Rochester

REPEATED
3:45 P.M.—
4:45 P.M.

MONDAY EVENING — BANQUET

TUESDAY, MAY 18

9:00 A.M.—
10: A.M. "Disease in Families: A Survey of the General Practice of Genetics"
Hymie Gordon, M.D., Rochester

10:00A.M.—
10:30 A.M. INTERMISSION
Visit Scientific and Technical Exhibits

10:30 A.M.—
12:00 Noon MAJOR COMPLICATIONS OF ACUTE CARDIAC INFARCTION
Presented by: Intensive Coronary Care Unit Committee of the Minnesota Heart Association and The Northlands Regional Medical Program.
Moderator: E. R. Giuliani, M.D., President-Elect, Minnesota Heart Association

10:30 A.M. "Heart Block"
Brian Campion, M.D., St. Paul

10:50 A.M. "Power Failure"
John Stokes, M.D., Rochester

11:10 A.M. "Rupture, VSD and Mitral Valve Dysfunction"
E. R.Giuliani, M.D., Rochester

11:30A.M.—
12:00 Noon ROUND TABLE DISCUSSION

12:15 P.M. LUNCHEON
Gregg Orwoll, Attorney, Rochester
"LAW AND MEDICINE—CONTINUING CONFLICT"

1:30 P.M.—
5:00 P.M. ALCOHOLISM AND DRUG ABUSE FORUM
Moderator: Donald H. Petersen, M.D., Willmar
Participants: Rev. John E. Keller, Chicago
Rev. Philip Hansen, White Bear Lake
Richard O. Heilman, M.D., Minneapolis
Milton O. Kepler, Jr., M.D., Univ. of Nebraska, Omaha, Nebraska
Graham B. Blaine, Jr., M.D., Harvard University, Cambridge, Massachusetts
Philip M. Margolis, M.D. Ann Arbor, Michigan

WORKSHOPS

2:00 P.M.—
3:00 P.M. 1) "L-Dopa"
Manfred D. Muenter, M.D., Rochester

2) "Surgical Emergencies in the Newborn"
Bernard J. Spencer, M.D., Minneapolis
Hugh B. Lynn, M.D., Rochester

3) "Handling and Moving the Injured Patient"
S. R. Maxeiner, Jr., M.D., Minneapolis
Phillip E. Richards, State Dept. of Healtl

REPEATED
3:45 P.M.—
4:45 P.M.

WEDNESDAY MORNING, May 19—Arranged by:

Minnesota Chapter of American College of Surgeons
Lyle J. Hay, M.D., President, Minnesota Chapter American College of Surgeons, Presiding

TRAUMA—PART I

9:00 A.M. "Facial Fractures and Injuries
John N. Simons, M.D., Rochester

9:10 A.M. Discussion

9:20 A.M. "The Early Management of Burns"
James W. LaFave, M.D., St. Paul

9:30 A.M. Discussion

9:40 A.M. "Treatment of Fingertip Injuries"
James H. Dobyns, M.D., Rochester

9:50 A.M. Discussion

10:00 A.M. INTERMISSION

TRAUMA—PART II

S. R. Maxeiner, Jr., M.D., Minneapolis, Presiding

10:30 A.M. "Initial Treatment of the Patient with Multiple Injuries"
John F. Perry, Jr., M.D., St. Paul

10:45A.M. "Trauma and the Lung"
Richard L. Simmons, M.D., Minneapolis

11:00 A.M. "Management and Prevention of Renal Failure in Trauma"
Fred L. Shapiro, M.D., Minneapolis

11:15 A.M.-**PANEL**—Questions and Discussion

12:00 Noon Albert Mowlem, M.D., Moderator, St. Paul
Panelists: John F. Perry, Jr., M.D.
Richard L. Simmons, M.D.
Fred L. Shapiro, M.D.

For Insomnia... one capsule for the rest of the night

NOLUDAR® 300



(methyprylon)

Before prescribing, please consult complete product information, a summary of which follows:
INDICATION: Relief of insomnia of varied etiology.
CONTRAINDICATIONS: Patients with known hypersensitivity to the drug.
WARNINGS: Caution patients about combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle shortly after ingesting the drug.
Physical and Psychological Dependence: Physical and psychological dependence rarely reported. If withdrawal symptoms do occur they may resemble those associated with withdrawal of barbiturates and should be treated in the same fashion. Use caution in administering to individuals known to be addiction-prone or those whose history suggests they may increase the dosage on their own initiative. Repeat prescriptions should be under adequate medical supervision.
Usage in Pregnancy: Weigh potential benefits in pregnancy, during lactation, or in women of childbearing age against possible hazards to mother and child.
PRECAUTIONS: If sleeplessness is pain-related, an analgesic should also be prescribed. Perform periodic blood counts if used repeatedly or over prolonged periods. Total daily intake should not exceed 400 mg, as greater amounts do not significantly increase hypnotic benefits.
ADVERSE REACTIONS: At recommended dosages, there have been rare occurrences of morning drowsiness, dizziness, mild to moderate gastric upset (including diarrhea, esophagitis, nausea and vomiting), headache, paradoxical excitation and skin rash. There have been a very few isolated reports of neutropenia and thrombocytopenia; however, the evidence does not establish that these reactions are related to the drug.

Each capsule contains 300 mg of methyprylon.

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To: Physicians in our Home State of Minnesota

From: Ulmer Pharmacal—Minneapolis

Subject: Our New Product—
ALPRINE BITABS

Alprine®

BITABS

A COMBINED GENTLE SEDATIVE-ANALGESIC

Each "two-layer" tablet contains:

Butalbital*	50 mg.
Phenacetin	130 mg.
Aspirin	200 mg.
Caffeine Alkaloid	40 mg.

***Warning:** May be habit forming.

Caution: Federal law prohibits dispensing without prescription.

ACTION AND USES: ALPRINE provides a combined gentle sedative-analgesic action to bring rapid relief from tension headache. Relieves pain due to muscular tension as in myalgia, sciatica, neuralgia, arthralgia.

ALPRINE helps control pain and discomfort in upper respiratory infections; i.e., coryza and sinusitis.

In the field of gynecology and obstetrics, ALPRINE combats the pain and possible depression accompanying dysmenorrhea. ALPRINE is indicated in postpartum pain and discomfort. Also may be used to relieve post-operative pain.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients.

PRECAUTIONS: Due to presence of a barbiturate, may be habit forming. Excessive or prolonged use should be avoided.

SIDE EFFECTS: In rare instances, drowsiness, nausea, constipation, dizziness, skin rash may occur.

WARNING: Used in excessive amounts and/or over a long period may affect the kidneys. Therefore, ALPRINE should not be taken in more than the recommended dosage nor for longer than a 10-day period without consulting the physician. Keep out of children's reach.

ADULT DOSAGE: 1 to 2 tablets repeated if necessary, up to 6 per day or as directed by physician.

SUPPLIED: Bottles, 100 tablets NDC 127-3012-01
Bottles, 1000 tablets NDC 127-3012-11

Division Physicians and Hospitals Supply Co.,

THE ULMER PHARMACAL COMPANY

Minneapolis, Minnesota 55403

To: Physicians in our Home State of Minnesota

From: Ulmer Pharmacal—Minneapolis

Subject: Our New Product—
DECONGESTCAPS



- **Relieves sneezing and sniffing.**
- **Opens airways for easier breathing.**
- **Controls excessive secretion.**
- **Provides 24 hours relief with B.I.D. dosage.**
- **Reasonable cost to patient.**

Decongestcaps T.M.

DECONGESTANT – ANTIHISTAMINIC – ANTICHOLINERGIC

By combining established antihistaminic, decongestant and anticholinergic medication in an extended release form, it is possible to bring continuous relief from rhinnorheic distress with only one capsule q. 12 h.

Each "extended release" capsule contains:

Chlorpheniramine Maleate . . . 8 mg.

Phenylpropanolamine Hydrochloride . . . . . 50 mg.

Atropine Sulfate . . . . . 0.36 mg.

Caution: Federal law prohibits dispensing without prescription.

ACTIONS: Decongestcaps offer fast and sustained relief from nasal congestion, watery eyes, excessive sneezing, running nose and post-nasal drip associated with the common cold, influenza, allergic rhinitis (hay fever, rose fever) and sinusitis.

Used in the recommended dosage, "extended release" of combined antihistaminic, decongestant and anticholinergic actions may keep the patient symptom-free both day and night.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients. Other deterrents include glaucoma, stenosing peptic ulcer, prostatic hypertrophy and gastric, pyloric or bladder stricture.

PRECAUTIONS: Should be used with caution in patients suffering from hypertension, hyperthyroidism, arterial disease, or organic heart disease. Patients who operate machinery or vehicles should be warned of possible drowsiness.

ADVERSE REACTIONS: Drowsiness, oral and nasal dryness, blurred vision, dizziness, irritability, tightness of chest, abdominal pain, disturbed coordination, palpitation, anorexia, urinary difficulty, tremor and insomnia may occur.

DOSAGE AND ADMINISTRATION: Adults and children over 6: One Decongestcap capsule q. 12 h. morning and at bedtime can usually give 24-hour relief. Generally contraindicated for children under six years of age. If significant adverse reactions occur, dosage should be reduced to one capsule at bedtime; if adverse reactions are more severe, medication should be discontinued.

HOW SUPPLIED: Bottles of 100 Capsules — NDC 127-2590-01
Bottles of 1000 Capsules — NDC 127-2590-11

Division Physicians and Hospitals Supply Co

THE ULMER PHARMACAL COMPANY

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he girth control pill



Tepanil® Ten-tab®

(continuous release form)

diethylpropion hydrochloride, N.F.)

When girth gets out of control, TEPANIL can provide sound upport for the weight control program you recommend. EPANIL reduces the appetite—patients enjoy food but eat ss. Weight loss is significant—gradual—yet there is a rela-vely low incidence of CNS stimulation.

ontraindicotions: Concurrently with MAO inhibitors, in patients hypersensitive to s drug; in emotionally unstable patients susceptible to drug abuse.

arning: Although generally safer than the amphetamines, use with great caution in tients with severe hypertension or severe cardiovascular disease. Do not use dur-g first trimester of pregnancy unless potential benefits outweigh potential risks.

dverse Reactions: Rarely severe enough to require discontinuation of therapy, un-easant symptoms with diethylpropion hydrochloride have been reported to occur relatively low incidence. As is characteristic of sympathomimetic agents, it may ccasionally cause CNS effects such as insomnia, nervousness, dizziness, anxiety, and jitteriness. In contrast, CNS depression has been reported. In a few epileptics an increase in convulsive episodes has been reported. Sympathomimetic cardiovascular effects reported include ones such as tachycardia, precordial pain, arrhythmia, palpitation, and increased blood pressure. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride; this was an isolated experience, which has not been reported by others. Allergic phenomena reported include such conditions as rash, urticaria, ecchymosis, and erythema. Gastrointestinal effects such as diarrhea, constipation, nausea, vomiting, and abdominal discomfort have been reported. Specific reports on the hematopoietic system include two each of bone marrow depression, agranulocytosis, and leukopenia. A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dry mouth, headache, dyspnea, menstrual upset, hair loss, muscle pain, decreased libido, dysuria, and polyuria.

Convenience of two dosage forms: TEPANIL Ten-tab tablets: One 75 mg. tablet daily, swallowed whole, in midmorning (10 a.m.); TEPANIL: One 25 mg. tablet three times daily, one hour before meals. If desired, an additional tablet may be given in midevening to overcome night hunger. Use in children under 12 years of age is not recommended.

T-107/4/71/U S PATENT NO 3,001,910

THE NATIONAL DRUG COMPANY
DIVISION OF RICHARDSON-MERRELL INC
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Painful night leg cramps...

unwelcome bedfellow for any patient– including those with arthritis, diabetes or PVD

One thing patients can sleep without, particularly patients with chronic disease conditions such as arthritis, diabetes or PVD, is painful night leg cramps. Although seldom the presenting complaint, night leg cramps can tie your patients up in painful knots. Now, just one tablet of QUINAMM at bedtime can usually bring an end to shattered sleep and needless suffering. Your patients will sleep restfully—gratefully—with QUINAMM, specific therapy to prevent painful night leg cramps.

Prescribing Informotion—Composition: Each white, beveled, compressed tablet contoins: Quinine sulfate, 260 mg., Aminophylline, 195 mg. **Indications:** For the prevention ond treatment of nocturnol ond recumbency leg muscle cromps, including those assocloted with orthritis, diobetes, voricose veins, thrombophlebitis, orteriosclerosis ond static foot deformities. **Contraindicotions:** QUINAMM is controlndicoted in pregnoncy becouse of its quinine content. **Precautions/Adverse Reactions:** Aminophylline moy produce intestinal cromps in some instonces, ond quinine moy produce symptoms of cinchonism, such os tinnitus, dizziness, and gastrointestinal disturbance. Discontinue use if ringing in the eors, deofness, skin rosh, or visuol disturbances occur. **Dosage:** One tablet upon retiring. Where necessary, dosoge may be increosed to one tablet following the evening meol ond one toblet upon retiring. **Supplied:** Bottles of 100 and 500 toblets.

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(quinine sulfote 260 mg., ominophylline 195 mg.)

Specific therapy for night leg cramps

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NEW EXPANDING OPPORTUNITIES for family physicians and physicians specializing in pediatrics, internal medicine, anesthesiology; in medically-awakening community. Contemporary, automated, 105-bed, new hospital to be completed in the fall of 1970. Present hospital to be converted into long-term unit. Patient service area 50,000 people. Medical staff leading and supporting recruitment efforts. Excellent community location, forty miles equi-distant to Milwaukee or Madison. Complete educational, cultural and recreational facilities. A new medical-dental building and 130-bed skilled care nursing home being constructed adjacent to the new hospital ready for occupancy January, 1971. Immediate satisfaction in practice, income and family living. Special assistance if needed. Write or call Paul R. Glunz, M.D., Watertown Memorial Hospital, 1301 E. Main Street, Watertown, Wisconsin 53094; telephone 414-261-4210 for more information.

IMMEDIATE OPENING: Internist or General Practitioner to join six man multispecialty group in northeastern Wisconsin. Excellent professional opportunity to practice in a friendly community, only two actively practicing physicians (General Practitioners) in the community outside of our clinic. Salary commensurate with training and experience first year and then full partnership. Ideal, safe small city living for the family on scenic Lake Michigan with excellent fishing, boating and hunting. All this and still only 1½ hours drive to Milwaukee or 45 minutes to Green Bay or lovely Door County. For complete details contact Robert E. Myers, M.D., Garfield at 23rd, Two Rivers, Wisconsin 54241.

WANTED—A G.P. or Surgeon for a small town on Canadian Border. Area provides wonderful fishing and hunting, new golf course and Country Club. Clinic partnership offered with good earnings and vacation allowances. Draft deferment probable. Good hospital. For further information, Write Ted Rowell, Sr., Baudette, Minn. 56623.

EMERGENCY ROOM PHYSICIAN—16-man group in Green Bay, Wisconsin, establishing Emergency Room Department. Positions available. Salary open with available stockholder arrangement. Contact C. G. Novotny, M.D., West Side Clinic, Green Bay, Wisconsin 54303.

WANTED: General practitioners, Internist, Pediatrician, Orthopedic Surgeon, Ophthalmologist, Obstetrician and Gynecologist for the Bemidji Clinic of Bemidji, Minnesota. Outdoor sports advantage second to none. The Bemidji Clinic now consists of three general practitioners, one internist, two general surgeons, one obstetrician, one otolaryngologist. If interested contact Duane E. Carlson, Business Manager, Bemidji Clinic, Bemidji, Minnesota.

GENERAL SURGEON wanted by young 6-man GP group. College town 30 miles from St. Paul-Minneapolis. JCAH accredited hospital. Reply to J. C. Palmquist, M.D., River Falls Medical Clinic, River Falls, Wisconsin (715) 425-5322.

AVAILABLE: Well established General Practice for one or two physicians. Present physician is returning to graduate school. New, well equipped clinic located in a prosperous, progressive community of 1200, 28 miles from Downtown Minneapolis. Four hospitals in immediate vicinity. Any terms available. Contact R. E. Simms, Security State Bank of St. Michael, St. Michael, Minnesota. Telephone 612-673-2131.

FAMILY PRACTITIONER OR INTERNIST to join congenial four man group. Partnership after one year. Laboratory and X-ray. Donovan L. Beckman, M.D., 1239 Payne Avenue, St. Paul, Minn. 55101. Call (612) 771-5577.

GENERAL PRACTITIONER urgently needed to join a well established practitioner. Excellent hospital and clinic facilities, Greenbush, Minnesota. Salary open and early partnership. Call collect 782-5275 or 782-4725.

GENERAL PRACTITIONER wanted for four man group with Board surgeon associated with community sponsored prepayment plan in NE Minnesota; hay fever haven; accredited hospital with radiologist, pathologist & internist services next door to modern clinic; good schools, swimming pool, indoor ice arena, golf, hunting, fishing, liberal salary $22,000-$25,000 first year; full partnership 6 months; equitable rotating call schedule & immediate work load. Write Medical Director, Community Clinic, Two Harbors, Minnesota 55616.

INTERNIST NEEDED: To join 9-man, all specialty group of 2 Internists, 2 Surgeons, 2 OB/GYN, 3 Pediatricians. City of 40,000 located 1-hour drive from Milwaukee on Lake Winnebago which serves a medical area of 75,000. Single hospital of 350 beds. Area affords excellent summer and winter recreational facilities. Superior schools, public and parochial and 2 colleges. Excellent initial salary leading to partnership in one year. For further information phone or write: W. G. Kendell, M.D., The Sharpe Clinic, S.C., 92 E. Division Street, Fond du Lac, Wisconsin 54935; Tel. (414) 921-0560.

ST. LOUIS PARK—new medical suites in Meadowbrook Medical Building directly connected by passageway to the Methodist Hospital. Phone 612-929-2633 Mr. Hirsch, or write Meadowbrook Medical Building, Leasing Office, 6490 Excelsior Boulevard, St. Louis Park, Minnesota 55426.

(Continued to Page 370)

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o over, whatever the therapy used, ordinary tests can be thrown off by such factors as rmal thyroid-binding protein levels, oral contraceptive use and pregnancy. A new od of assessment—the Free Thyroxine Index (FTI)**—helps eliminate these errors. By ng measurements of total and protein-bound T_4, the FTI indicates your patient's status sely. And with Euthroid, the precision of your diagnosis is matched by the precision ur therapy.

sest in clinical effect to human endogenous thyroid

oid provides both T_4 and T_3 in the optimum *oral* ratio of 4:1 by weight and in proper amounts, closely simulating endogenous thyroid in clinical effect. Dose response can sessed unequivocally through use of the FTI—and because we want you to put Euthroid test *with this most rigorous of tests,* we offer you an aid to easier determination:

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nger does FTI determination require you to perform lengthy mathematical exercises. the Euthroidex calculator—another first from Warner-Chilcott—you compute it easily curately... almost instantly. Send for yours now.

roid therapy, Euthroid offers you the calculated success—and the calculator to go with it.

To request your Euthroidex™ calculator (with booklet explaining its use and rationale for the FTI), just write "Euthroidex" on your imprinted card, prescription blank or stationery, and mail to Warner-Chilcott, Morris Plains, N.J. 07950.

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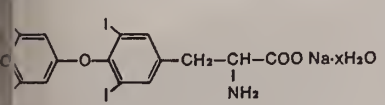
sodium levothyroxine (T_4) sodium liothyronine (T_3)

F., and Horn, D. B.: Assessment of thyroid function by mbined use of the serum protein-bound iodine and resin uptake of liiodothyronine, J. Clin. Endocrinol. 25:39 (Jan.) 1965.

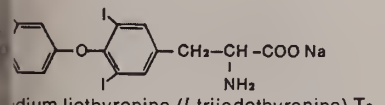
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on: Federal law prohibits dispensing ut prescription.

oid is synthetic microcrystalline sodium hyroxine (T_4) USP and synthetic micro- alline sodium liothyronine (T_3) USP com- l in a constant 4:1 ratio.



dium levothyroxine (*l*-thyroxine) T_4



dium liothyronine (*l*-triiodothyronine) T_3

ons: Euthroid provides replacement ther- for the thyroactive material normally lied by the human thyroid. The normal id gland produces and stores thyro- ulin, the active components of which are metabolically active hormones: *l*-thy- e and liothyronine. Euthroid (liotrix) pro- a combination of these hormones in ied, synthetic form, supplied in a con- 4:1 ratio in order to simulate as closely ossible the physiologic and metabolic ts of normal endogenous thyroid secre-

contrast with the individual synthetic, bolically active hormones, Euthroid will lly produce normal results for PBI, T_3, other thyroid function tests—consistent clinical progress—when persons with genous thyroid deficiencies are made yroid. Sodium liothyronine (T_3) acts more dly and for a shorter period of time than arations of biological origin. Custom- , its use as a single agent produces in- opriately decreased PBI values. Sodium thyroxine (T_4), on the other hand, is more ly bound by plasma protein fractions and somewhat slower acting than sodium yronine (T_3); its use as a single agent ls to produce inappropriately elevated values. Euthroid, with its unvarying 4:1 of T_4/T_3, permits interpretation of ap- priate laboratory tests consistent with the l clinical status of the patient.

cations: Euthroid (liotrix) provides thyroid acement therapy in all conditions of in- quate production of thyroid hormones, namely:

1) Hypothyroidism, including cretinism and myxedema.
2) Simple (nontoxic) goiter.
3) Subacute or chronic thyroiditis including Hashimoto's disease.
4) Prevention of goiter in hyperthyroid patients undergoing treatment with thiouracil derivatives.
5) Usage in patients who may manifest intolerance to thyroid products of animal origin.

Contraindications: Acute myocardial infarction, adrenal insufficiency, hypersensitivity to any component of this drug.

Warnings: Liotrix should not be used in the presence of cardiovascular disease unless thyroid replacement therapy is clearly indicated. If the latter exists, low doses should be instituted (Euthroid-1/2 or Euthroid-1) and increased by the same amount in increments at 2-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out and adrenal deficiency due to hypopituitarism corrected before liotrix therapy is started.

If hypothyroidism and adrenal insufficiency exist concomitantly, cortisone or similar steroids should be given at dose levels sufficient to correct the adrenal insufficiency before attempting replacement therapy with thyroid hormones.

Likewise, the possibility of alterations in the prothrombin time must be considered and closely monitored in patients on anticoagulant therapy.

Myxedematous patients are very sensitive to thyroid hormones, and dosage should be started at a very low level and increased gradually.

Precautions: Hypothyroid patients are especially sensitive to thyroid preparations, and those with severe hypothyroidism may be unusually so.

Initiation of thyroid replacement therapy in patients with diabetes must be carefully monitored because of potential fluctuation in daily insulin or oral hypoglycemic requirements.

As with all thyroid preparations, this drug will alter the results of thyroid function tests.

Adverse Reactions: Overdosage or too rapid increase in dosage of thyroid preparations can produce signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration: Initial dosage should be low and gradually increased at 2-week intervals until the desired clinical response is obtained.

Laboratory criteria of euthyroidism include a PBI of 3.5 to 8 mcg; T_3, T_4, and BEI tests are useful.

For most patients, a single daily dose of Euthroid-1, -2, or -3 will maintain euthyroidism. Transfer of a patient from a maintenance dose of another thyroid preparation to Euthroid can usually be effected smoothly. See table for initiating therapy or converting from other thyroid preparations.

Euthroid (liotrix)	Approximate Equivalents Natural	Synthetic	
Tablet	T_4*/T_3** mcg	Thyroid USP	T_4*	T_3**
Euthroid-½ pale orange	(30/7.5)	½ grain	.05 mg	12.5 mcg
Euthroid-1 light brown	(60/15)	1 grain	.1 mg	25.0 mcg
Euthroid-2 violet	(120/30)	2 grains	.2 mg	50.0 mcg
Euthroid-3 gray	(180/45)	3 grains	.3 mg	75.0 mcg

*T_4=sodium levothyroxine (*l*-thyroxine)
**T_3=sodium liothyronine (*l*-triiodothyronine)

Dosage for cretinism or severe hypothyroidism in children is the same as for adults with myxedema. Eventual maintenance dosage in the growing child may be higher than in the adult.

Overdosage: *Symptoms*—Headache, instability, nervousness, sweating, tachycardia, and unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm; chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

Treatment—Shock—Supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.

Supplied: Square W/C monogrammed tablets of four potencies, each identified by a different color (see table); bottles of 100 and 1000.

E-GP-11-4C

WARNER-CHILCOTT Morris Plains, N.J. 07950

Classified Advertisements

(Continued from Page 367)

WANTED: GENERAL PRACTITIONER, out of internship or established. Green Bay, Wisconsin (Population 100,000). New clinic for 3 man G-P group. Laboratory, X-Ray, EKG, 2 registered lab technicians, 2 registered nurses, complete office staff. Present partners, ages 57 and 47. Large enough practice for 3 men now. Two Catholic and 1 Protestant hospitals, staff open. Schools both parochial and public are excellent. One university and one college. In heart of boating, fishing, hunting, skiing and snowmobile country. Have symphony orchestra and within easy driving to Milwaukee and Chicago. Jet service daily. Need younger GP to work with us, not for us. Salary open, no investment. We need you badly—two Packer season tickets to sweeten things! Contact R. J. Rose, M.D., or R. E. Jensen, M.D., 621 East Walnut Street, Green Bay, Wis. Call 437-4366.

TEN MAN MULTISPECIALTY group needs an ophthalmologist and another pediatrician. New clinic building, complete laboratory and x-ray facilities. 180 bed modern hospital across street from clinic. Early share-holder status. Salary open. Write or call the Lenont-Peterson Clinic, Ltd., C. A. Tietz, M.D., area code 218, 741-4292, Virginia, Minnesota 55792.

ONE HAMILTON Examining table, 1-15 m-amp portable x-ray, One instrument-table autoclave, One short wave diathermy. All are in excellent condition. Write: Dr. L. K. Onsgard, Houston, Minnesota.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul 55101.

TWO GENERAL PRACTITIONERS, office adjoining Fairview Southdale Hospital, desire doctor to work all or part of June, July and August, 1971. ($500.00 per week plus percentage.) Permanent association possible. Contact: Doctors Krafft and Dornbach, 200 Southdale Medical Building, Edina, Minnesota 55435; Phone: 920-8060 (Area code 612).

POSITIONS WANTED. Have talent. Will travel. June graduates of the MLA (CLA) program of the Hibbing Area Technical Institute will fulfill the needs of your laboratory. Contact Charlotte Sandstrom, Instructor, Hibbing Area Technical Institute, Hibbing, Minnesota. Phone 218-262-3824.

WANTED LOCUM TENENS: Three-man Minneapolis GP group desires physician with Minnesota license to work parts of the summer of 1971. Salary and conditions excellent. CONTACT 529-9251.

INTERNIST OR GENERAL PRACTITIONER FOR Medical Svc or Outpatient Dept in 235 bed GM&S Hospital in beautiful southern Black Hills. Fully accredited, well-staffed and equipped. Salary range $22,000 to $28,000 depending on qualifications. Excellent Federal employee benefits. May be licensed in any state. On station quarters available. Ideal family living. Area abounds in outdoor recreation. Climate surprisingly mild. Equal opportunity employer. Contact: Chief of Staff, VA Center, Hot Springs, So. Dak. 57747.

OB/GYN—PEDIATRICIAN—INTEREST, Mpls.-St. Paul. Midwest's leading prepaid group offers high standards, excellent earnings, no investment. Generous vacation and conference leave, fully paid insurance and retirement, time for teaching and professional pursuits. A. F. Anderegg, M.D., 612-645-5851, 2500 Como Ave., St. Paul, Minn. 55108.

TROUT STREAM FRONTAGE on Cascade River. Also Forest and Meadow Cabin Sites. N. Shore, in Forest, 2 mi. to Pike L. boat launch area, 3 mi. to Lake Superior, 10 mi. to town, Cook County. Airport N. of town. Long term lease. L. Scherer, Jr., Lutsen, Minn. 55612.

IMMEDIATELY AVAILABLE. Excellent practice in West Central Minnesota college town of 5,300. Practice area easily 15,000. Beautifully equipped modern hospital, staffed by family physicians with immediate consulting staff in Surgery, Internal Medicine, Urology, and Radiology. Physician is closing his office to become Director of Health Service at the University. *MUST* sell by July 15th. Will consider *any* financial arrangement. Write or call Collect, Robert M. Watson, M.D., 106 East Sixth Street, Morris, Minnesota 56267. Phone 612-589-2611 or (home) 589-1221.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D., Chippewa Falls, Wisconsin.

THE MIDELFORT CLINIC is seeking associates in the following areas: (1) Internal Medicine, (2) Orthopedic Surgery, (3) Obstetrics-Gynecology. This is an opportunity to join a 24-man group which has been organized since 1927. We have a new clinic building, excellent hospital facilities, and are located in a college community. For further information, contact D. R. Griffith, M.D., President, Midelfort Clinic, Ltd., Eau Claire, Wis. 54701.

36 HOUR WEEK, NO NIGHT CALLS, downtown Minneapolis. Mainly executive and professional clientele. Physical examinations, minor ailments, out-patient care. Minimum start $24,000 plus bonuses, state salary desired if specially qualified. Write: MINNESOTA MEDICINE-455, 385 Jackson St., St. Paul, 55101.

Books Worth Having

Cancer: Diagnosis, Treatment & Prognosis—*Lauren V. Ackerman & Juan A. del Regato.* C. V. Mosby Co., 1970—Pages 1,049

Illustrations: 783. Price: $39.50

This is an excellent reference for all types of cancer. The illustrations and graphs are pertinent, and at the end of each subject there is an adequate list of bibliographic references. An excellent book.

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University of Minnesota

Office of Postgraduate Educational Activities • College of Medical Sciences

May

May 10-11.....Diseases of the Cornea
May 12-14 ..Laboratory Medicine: Current Concepts of Streptococcal Disease
May 24-26 .....Anesthesiology
May 24-26 .....Breast and Endocrine Surgery
May 24-26 .....Anesthesiology for Family Practitioners

June

June 1-4 .....Current Concepts in Radiation Therapy

For further information concerning the above listed programs and opportunities contact: Office of Postgraduate Educational Activities, Box 193, Health Sciences Center, University of Minnesota, Minneapolis, Minnesota 55455.

Precision is a natural goal when you prescribe thyroid replacement therapy.

When you prescribe Proloid (thyroglobulin) you specify a precision blend of the two natural active hormones—T_4 and T_3—in their natural protein, *thyroglobulin.*

It's because Proloid is the natural thyroid hormone-globulin complex extracted and purified of unnecessary glandular debris.

91 control tests, 2 clinical assays: Beginning with the USP iodine assay and continuing through chromatographic analysis for T_4 and T_3 content and includi testing in hypothyroid humans—Proloid is made as pr cise as the natural product can get, batch after batc

New 2 grain tablet: Precision extends to dosage. Wi the introduction of a new 2 grain tablet, titration c be even more conveniently achieved with the full ran of Proloid dosages: *¼, ½, 1, 1½, the new 2, 3, ar 5 grain tablets.*

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as close to precision as the natural can get

Proloid®
(thyroglobulin)
the natural for precision

Proloid® (thyroglobulin)

Description: Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, sodium levothyroxine (T_4) and sodium liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.

Chromatographic analysis to standardize the sodium levothyroxine and sodium liothyronine content of Proloid (thyroglobulin) is routinely employed.

The ratio of T_4 and T_3 in Proloid (thyroglobulin) is approximately 2.5 to 1.

Proloid (thyroglobulin) is stable when stored at usual room temperature.

Indications: Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.

Contraindication: Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.

Warnings: Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid, and dosage should be started at a very low level and increased gradually.

Precaution: As with all thyroid preparations this drug will alter results of thyroid function tests.

Adverse Reactions: Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration: Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, T_3 ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.

Instructions for Use: The following conversion table lists the approximate equivalents of other thyroid preparations to Proloid (thyroglobulin) when changing medication from desiccated thyroid, T_4 (sodium levothyroxine), T_3 (sodium liothyronine), or T_4/T_3 (liotrix).

Dose of Proloid (thyroglobulin)	Dose of desiccated thyroid	Dose of T_4 (sodium levothyroxine)	Dose of T_3 (sodium liothyronine)	Dose of liotrix (T_4/T_3)
1 grain	1 grain	0.1 mg	25 mcg	#1 (60 mcg/ 15 mcg)
2 grains	2 grains	0.2 mg	50 mcg	#2 (120 mcg/ 30 mcg)
3 grains	3 grains	0.3 mg	75 mcg	#3 (180 mcg/ 45 mcg)
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.

Overdosage Symptoms: Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(**Treatment:** In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

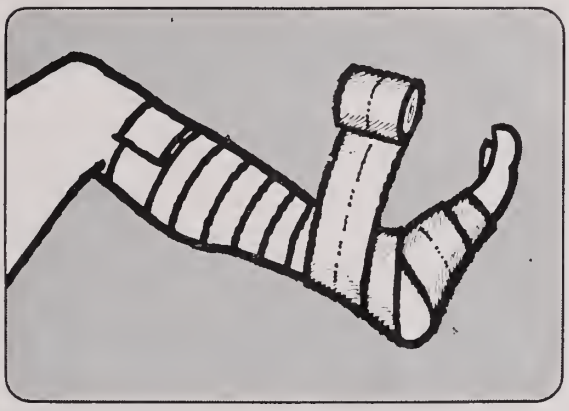
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There is no guarantee of safety, even with Erythrocin.

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See next page for brief summary, listing indicated organisms, precautions, etc.

Erythrocin®

(ERYTHROMYCIN, ABBOTT)

Brief Summary

Indications

Erythrocin is indicated against gram-positive cocci — staphylococci (most strains), pneumococci and streptococci (including enterococci). Active against other pathogens, such as *Corynebacterium, Hemophilus, Clostridium, Neisseria,* and *Treponema pallidum,* the agents causing trachoma and lymphogranuloma venereum and primary atypical pneumonia caused by *Mycoplasma pneumoniae* (Eaton agent). Establish susceptibility of pathogenic organism when practical. Maintain therapeutic levels for ten days in the treatment of streptococcal infections to help prevent rheumatic fever and glomerulonephritis. Also consider local measures or surgery whenever indicated.

Contraindications

Known hypersensitivity to erythromycin. I.M. preparation also contraindicated in patients hypersensitive to the "caine" type of local anesthetics.

Precautions, Side Effects

Occasionally abdominal discomfort, cramping, nausea or vomiting may occur; generally controlled by reduction of dosage. Mild allergic reactions, such as urticaria and other skin rashes, may occur. Serious allergic reactions have been extremely infrequent; if hypersensitivity is encountered consider appropriate countermeasures, e. g., epinephrine, steroids, etc., and withdraw drug. The rare possibility of overgrowth of nonsusceptible organisms should be kept in mind; if it occurs withdraw drug and institute appropriate treatment. Local venous discomfort, generally mild, may occur with I. V. administration. I.M. preparation is suitable for deep intramuscular administration only; restrict use in children with small muscle mass. A mild transient local discomfort sometimes occurs following rectal insertion of Erythrocin Suppositories; discontinue if significant discomfort persists.

Administration and Dosage

I. ORAL: In adults with mild to moderate infections caused by readily-susceptible organisms 1.0 Gm. daily; more severe infections or those caused by less susceptible organisms 2.0 Grams daily; unusually severe infections up to 4 or more Gm./day. Daily dose in children is 15 to 25 mg./lb./day depending upon severity of infection. Daily dose should be administered in divided doses at 4-to-6 hour intervals. Continue treatment for at least 48 hours after symptoms have subsided and temperature has returned to normal. In fulminating or life-threatening infections, a parenteral form of erythromycin is preferred.

II. PARENTERAL: Intravenous administration may be continuous or intermittent (6 to 8 hour intervals); 1 to 4 Gm. daily in adults; 15 to 25 mg./lb./day in children, depending upon severity of infection. Recommended I.M. dose is 100 mg. (2 ml.) for adults, 50 mg. (1 ml.) for children 30 lbs. or more and 1.4 to 1.8 mg./lb. in smaller children. Injections are usually given at 6 to 8 hour intervals; may be given at 4 to 6 hour intervals for severe infections.

III. RECTAL: Following therapeutic doses are recommended in children: to 20 lbs., 1-125 mg. suppository every 8 hours; 20 to 40 lbs., 1-125 mg. suppository every 6 hours.

Change to oral therapy as soon as practicable.



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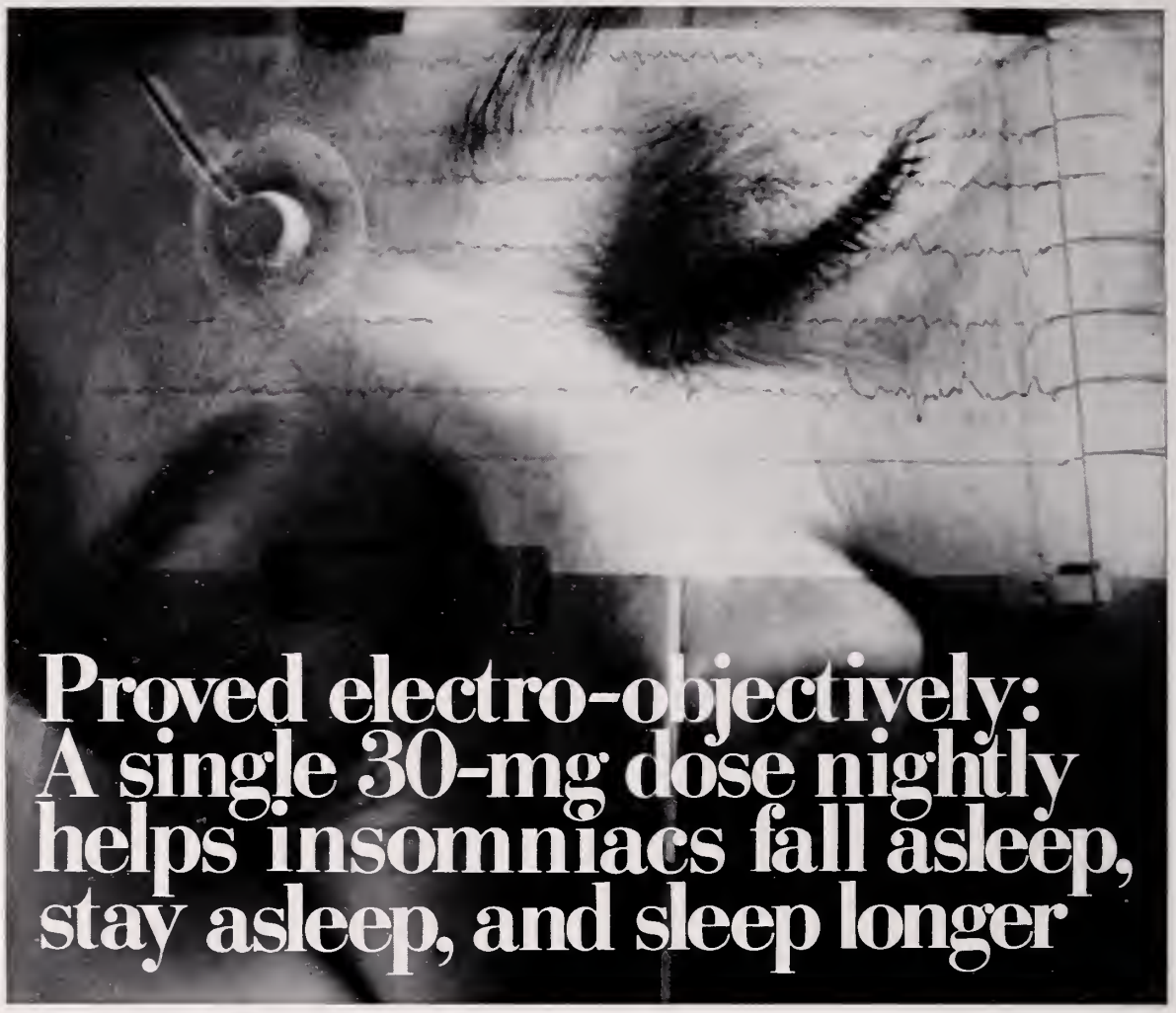


University of Sydney — *Professor Charles Kerr*

JUNE, 1971

Special Issue

University of Sydney, Australia



Proved electro-objectively: A single 30-mg dose nightly helps insomniacs fall asleep, stay asleep, and sleep longer

Controlled studies of 23 insomniac and 13 normal subjects treated with Dalmane (flurazepam HCl) in five sleep laboratories generated over 4000 hours of electroencephalographic, electro-oculographic and electromyographic tracings. These studies revealed that Dalmane 30 mg nightly usually induces sleep in 22 minutes and provides seven to eight hours of sleep.[1,2,3]

Moreover, Dalmane 30 mg was found to be useful in all common types of insomnia in which it was studied. Of drugs studied in a sleep laboratory,[1] Dalmane 30 mg was the only one that consistently reduced sleep induction time and maintained sleep nightly for 14 consecutive nights of use.

Confirmed clinically

Fifty-three controlled studies using a paired-night, double-blind crossover design have evaluated Dalmane clinically. In the majority of these, Dalmane (flurazepam HCl) significantly reduced sleep induction time and increased sleep duration. Dalmane and a placebo were alternated on successive nights in 2010 insomniacs, 1706 of whom were studied for a single night-pair, and the remainder for as many as fifteen paired-nights. A patient preference for Dalmane was apparent in the paired-night studies.

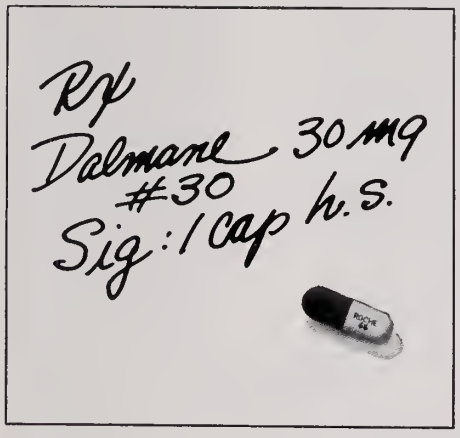
Dalmane was also preferred to certain hypnotics in two separate preference studies. In each of two double-blind studies, Dalmane 30 mg retained effectiveness for the total period of seven consecutive treatment nights, according to subjective/objective evaluations.

In summary, Dalmane is useful in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening. It can be used effectively in patients with recurring insomnia or poor sleeping habits, and in acute or chronic medical situations requiring restful sleep.

Dalmane (flurazepam HCl) is generally well tolerated

In most instances in which adverse effects with Dalmane were reported, they were mild, infrequent and seldom required discontinuation of the drug. Dizziness, drowsiness, lightheadedness and the like were the side effects most frequently noted, particularly in elderly or debilitated patients.[3] Instances of hepatic dysfunction, paradoxical reactions (excitement) and hypotension are rare with Dalmane, and morning hang-over is relatively infrequent. In studies to date the effectiveness of Dalmane for recommended periods of use is maintained without need to increase dosage.

References: 1. Kales, A., *et al.:* "Effectiveness of Sleep Medications: All-Night EEG Studies of Hypnotic Drugs," in Proc. 7th Internat. Cong. Electroencephal. and Clin. Neurophysiol., San Diego, Calif., Sept. 13-19, 1969. **2.** Kales, A., *et al.:* "Psychophysiological and Biochemical Changes Following Use and Withdrawal of Hypnotics," in Kales, A. (ed): *Sleep: Physiology and Pathology,* Phila., Lippincott, 1969, p. 331. **3.** Data on file, Medical Department, Hoffmann-La Roche Inc.



For the sleep your patients need

New **Dalmane®**
(flurazepam hydrochloride)

Before prescribing, please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.,* operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.,* excitement, stimulation and hyperactivity, have also been reported in rare instances.

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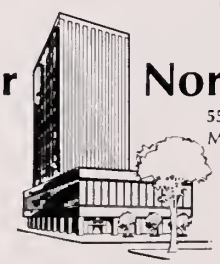
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President's Letter

As your new president, I look forward, with enthusiasm, to the forthcoming year. We are now reaching the midpoint of what many term the "Health Year." Numerous favorable as well as unfavorable comments have been made regarding the health care of our nation; never before has organized medicine been as challenged to provide leadership and programs in wide and diversified areas of health care.

Your Minnesota State Medical Association is intimately involved in the problems of health care. We have provided some of the initial data to be used in the implementation of comprehensive prepaid health care plans. These plans are administered by private health insurance companies and provide health services to the subscriber on a fee for service-free choice of physician concept. There are other plans in operation that provide for comprehensive service on a closed panel-per capitation-monthly rate concept. There are also many other plans that provide health care with an initial deductible clause and major medical protection. The officers of your State Medical Society are thoroughly informed regarding these various health care plans. They can provide guidance to any physician or group of physicians who wish to provide leadership in health care delivery systems in their community.

Health manpower distribution is another serious problem for our state. The University of Minnesota Medical School has increased its enrollment by approximately 65 students for each new class. The curriculum and programs for training these students have been changed, drastically, but will not be successful without the cooperation of the members of our State Medical Association. We must provide additional educational opportunities for these students in our own private practice. By doing this, it is hoped that more students will be interested in remaining in Minnesota to practice and raise their families.

In order to make new programs successful, the officers and council of your State Medical Association will need the cooperation and help of each member and specialty group in our state. We want our patients to feel that when they are ill, they will get first class medical care. I am sure the concern of all the doctors in Minnesota is to provide the best medical care possible to the people of our state.

We must continue to improve communication between our membership and officers of our society, as with productive dialog, many new and innovative ideas can be promptly and successfully implemented.

I wish to join our editor-in-chief, Doctor Carl O. Rice, in paying tribute to our Australian colleagues for their enlightening contributions to this issue of Minnesota Medicine.

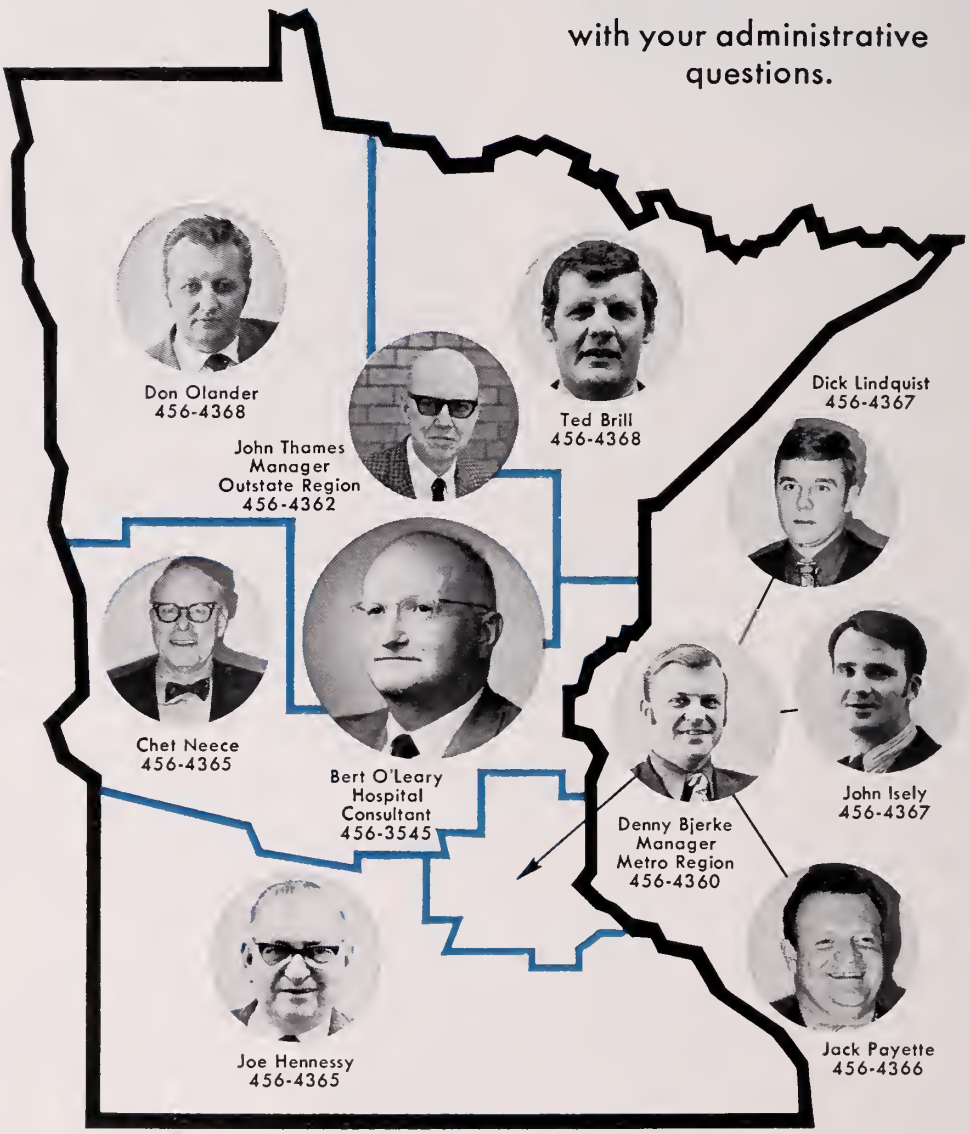
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Greetings

That great complex of achievement we call civilization and the miracle of life itself are dependent for their existence and continuing vitality on basic communications systems.

Recent research in fields as diverse as biochemistry, politics and business management has revealed an intriguing point of convergence. Researchers in each of these fields have placed increasing importance on the role of communication in the healthy functioning of an organism—whether that organism be a business firm, a government, a military operation or a brain cell. At all levels of life the collection and dissemination of data and decisions is a function that is essential to growth and development. The electronic computer, the political debate and the chemical communication systems of living cells are all vital components of our lives.

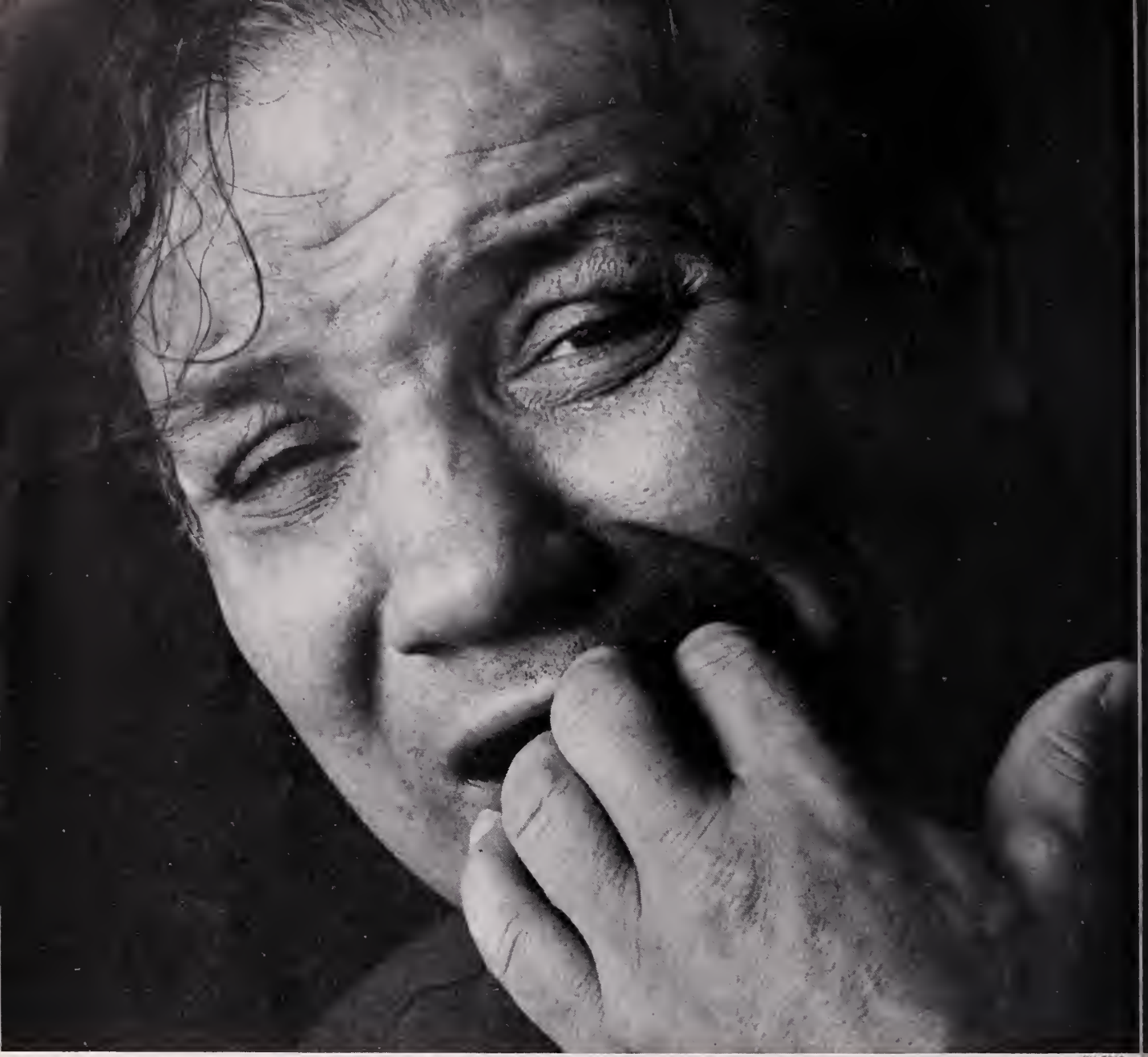
Despite the increasing interest in communications, the term itself is often misunderstood. Communication does not mean the mere transmission or dissemination of information; it also means *reception* and *response*. Communication is a dynamic process, not a passive one. It is a two-way affair: not a monologue, but a dialogue. It is only through dialogue, through the give and take of discussion that we can really communicate with our fellow man.

Given the tensions and problems of today's world, perhaps the most valuable dialogue we can engage in is that which promotes wider and deeper *international* understanding. The problems that face our world can be solved only by the cooperative endeavour of all peoples. And that is why I find so encouraging this issue of *Minnesota Medicine* which seeks to create a dialogue between members of the medical fraternities of Minnesota and New South Wales.

Medicine of course has always led the field in international communication and cooperation. Considering the problems that governments and business encounter in many aspects of international relations, it never ceases to arouse admiration and amazement to observe the speed with which advances in medical science are communicated to even the most remote and inaccessible corners of the earth.

As a Minnesotan, as a brother of the Editor-in-Chief of this Journal, and as one who is professionally engaged in the promotion of better international relations, it is with particular pleasure and pride that I extend my congratulations to the Sydney University Faculty of Medicine and the Minnesota Medical Association. I hope that ventures in communication and cooperation such as this will be continued and that this contribution to international relations will stand as an inspiration and example to others.

Walter L. Rice
American Ambassador to Australia



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Treatment of Chronic Peptic Ulcer

A Critical Appraisal

D. W. PIPER, M.D., F.R.A.C.P., M.R.C.P.*

CHRONIC PEPTIC ulcer continues to remain a medical problem which relates to a firm diagnosis as well as the clinician's dilemma in assessing the therapeutic approach to the patient. Though many aspects of therapy have been discussed in previous reviews,[1,2] the rapid progress in this field justifies the presentation of more recent data.

The Diagnosis of Chronic Peptic Ulcer

The diagnosis of a *duodenal ulcer* is a simple radiological procedure involving the demonstration of duodenal deformity or ulceration with a consistent clinical syndrome.

The diagnosis of chronic *gastric ulcer* involves two steps: first the demonstration of a gastric lesion, and second, the assurance that the lesion is benign. The utilization of large quantities of barium, as formerly used, has no place, as the air contrast technique[3] enables the mucosal pattern to be outlined and to be seen as readily as in the resected specimen. Demonstration of the benign nature of the lesion involves the use of exfoliative cytology,[4,5] gastric biopsy,[6] gastroscopy and gastric secretion studies. The use of these techniques should leave no doubt as to whether a gastric lesion is benign or malignant. The true nature of the lesion can be demonstrated in three to four days, with admission to hospital for only a few hours on each of these days. The response to a therapeutic trial, used as a diagnostic procedure, clearly has no place in modern-day medicine, though it must be emphasized that exfoliative cytology[4] will give false negative results in 30% of patients suffering from malignant ulcer. Using these diagnostic procedures for the past 10 years, we have had only one case where diagnostic doubt existed.

*Associate Professor of Medicine, The University of Sydney, and Honorary Physician, The Royal North Shore Hospital of Sydney.

Treatment of Peptic Ulcer

Bed Rest and Cessation of Smoking

The studies of Doll and his colleagues have convincingly shown that bed rest and cessation of smoking accelerates the healing of chronic gastric ulcer.[8,9]

Antacid Therapy

Antacid therapy, in the dosage used by most physicians in the past, could have scarcely more than a placebo effect. Myhill and Piper[10], and Piper and Fenton[11] determined the dose of antacid therapy that must be given to effectively neutralize the gastric contents, and subsequently Baume and Hunt submitted this dose to double blind clinical trial[12]. The latter results show that intensive antacid therapy failed to accelerate the healing rate of chronic gastric ulcer. Stiel, Mitchell, Radcliff and Piper found the hypercalcaemia rate in patients given large doses of calcium carbonate to be approximately 30%.[13] From these findings it must be concluded that intensive antacid therapy has no place in the treatment of peptic ulcer. It is, however, well demonstrated that antacids ease pain.[14] But for this purpose the relatively non-potent antacids are satisfactory. Sodium-containing and calcium-containing antacids in any form should not be used; numerous tablet preparations on the market fulfill the required criteria. Our current practice is to advise the patient to take antacids only when pain is felt and not on any fixed pattern or schedule.

Anticholinergic Drugs

A large number of anticholinergic drugs are available commercially, and it has been effectively demonstrated that some anticholinergic drugs will reduce gastric acid secretion. The anticholinergic glycopyrrolate (Robinul) reduces the recurrence rate of chronic duodenal ulcers[12,15,16] and will accelerate the

healing[12] of chronic gastric ulcers in hospitalized patients. When anticholinergic drugs are used, pharmacologically effective doses must be employed; i.e., day-time doses given one hour before each meal must be such that some side effects are present occasionally during the day, and the night-time doses must invariably produce some side effects on waking. Of the large number of preparations on the market, it is felt that only five anticholinergics have been adequately demonstrated to have an effect on gastric secretion and/or to alter the course of peptic ulcer. These are (listed alphabetically): glycopyrrolate (Robinul), isopropamide iodide (Tyrimide), oxyphencyclime hydrochloride (Daricon), poldine methysulphate (Nacton) and propantheline bromide (Probanthine).

These drugs are contraindicated in patients with pyloric stenosis, prostatic hypertrophy, reflux oesophagitis, or a history of glaucoma.

Though it is difficult to specifically advise the doctor with regard to anticholinergic drug therapy we feel that the evidence is adequate to justify its widespread use. If used generally, however, pharmacologically effective doses must be given, and both patient and doctor must be aware of potential side effects.

*Carbenoxolone Sodium (Biogastrone)**

The most interesting development in the treatment of gastric ulcer has been carbenoxolone sodium. In Europe, liquorice has been long used for the treatment of dyspepsia and its basis was subsequently investigated by the Dutch physician Revers; later, Biorex Laboratories* in the United Kingdom introduced a pure chemical compound, carbenoxolone sodium, which was considered responsible for the beneficial effects caused by liquorice. Double blind clinical trials disclosed that it exerted a beneficial effect on the healing of gastric ulcers.[7] The response obtained in ambulant patients is approximately equal to that obtained by bed-rest patients in the hospital. In duodenal ulcer, however, its effect has not been shown beyond all doubt to be beneficial.

Carbenoxolone sodium has the disadvantage of being relatively expensive and may cause water and sodium retention and/or hypokalaemia, especially if the dose of 300 mg per day is given. Consequently, if patients are given this drug, they should be observed closely for excessive weight gain and hypokalaemia. A dose of 50 mg three times daily, producing no side effects, is less effective in its healing action.

Efforts have been made to abolish the water and salt retention by thiazide diuretics, but in abolishing the water and salt retention, such diuretics increase the risk of hypokalaemia. Abolishing both the salt-retaining and the potassium-losing effect of carbenoxolone sodium by spironolactone is not feasible because spironolactone blocks both the side effects and the healing properties of carbenoxolone sodium.

The introduction of this drug which has a healing rate in the ambulant patient equivalent to that in bed-rest patients, raises the problem as to whether all patients should be treated by carbenoxolone sodium rather than be admitted to hospital for bed rest. Its chief application at the moment is in those patients who cannot afford bed rest or who are unwilling to be admitted to hospital. Until further evidence is available, carbenoxolone sodium is not indicated in the routine treatment of duodenal ulcer, nor is its use justified at present to prevent the recurrence of either chronic gastric or duodenal ulcer.

It appears there are two substances in liquorice, one that produces ulcer healing and the other, the accompanying metabolic disturbances; and attempts are being made to separate these. While it has ben claimed that a deglycerinised liquorice preparation† is therapeutically effective and devoid of side effects, acceptance of this preparation by the medical profession should await the results of further and larger double blind clinical trials.

The interested reader is referred to recent reviews for further information regarding carbenoxolone sodium.[18,19,20]

Sedation and Diet

Carefully controlled clinical trials have shown that sedation and diet are of no benefit in the treatment of peptic ulcer.[9,21,22] Salicylates should be avoided because they delay the healing of chronic gastric ulcer.[23]

*Biogastrone (Biorex Laboratories, London, U.K.).
†Caved-S (Cedona, Haarlem, Holland).

Concluding Comments

General Approach to the Therapy of Chronic Peptic Ulcer

It is essential that physicians adopt a positive approach towards the treatment of chronic peptic ulcer. No patient in any society, either affluent or underdeveloped, should be allowed to suffer the inconvenience, disability, mortality or morbidity of a chronic peptic ulcer. If circumstances permit, the patient should be treated as outlined above. After the ulcer has healed, the patient should be advised to lead a normal life, eat a normal diet, avoid smoking, and possibly be placed on long-term anticholinergic drug therapy. *If the ulcer recurs within two years, it should be assumed that the patient's ulcer diathesis is so great that medical treatment is unlikely to be of any avail and surgery should be advised.*

Surgery

If, as is the case in some undeveloped countries, medical treatment is economically impossible, the patient should have surgery at an early stage.

One of the major advances in the treatment of ulcer disease has been the success of modern surgery. Between the two great European wars, surgeons tended to excise more and more of the stomach, their goal being the abolition of stomal ulceration. This resulted in a large number of "gastric cripples" for whom no surgery or other treatment was of avail. Currently, gastrectomy is performed only for benign gastric disease in the case of chronic gastric ulcer where a Billroth I procedure is the operation of choice. For duodenal ulcer, there is no doubt that the surgery of choice is vagotomy plus some drainage procedure, either pyloroplasty or gastroenterostomy. It has been adequately demonstrated that the surgery of duodenal ulcer can have negligible mortality; a recent series of operations done by a group of surgeons reported 452 consecutive operations for duodenal ulcer without any operative deaths.[24]

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Which means far more to the fainting heart
Than shelter and bread and wine.
For shelter is gone when the night is o'er,
And bread lasts only a day,
But the touch of the hand and the sound of the voice
Sing on in the soul alway.

*Spencer Michael Free, (1856-1938), author of some five hundred poems, practiced medicine for almost fifty years in DuBois, Pennsylvania, and specialized in general surgery during his later years. His best known poem, The Human Touch, has been translated into twenty-six languages and quoted widely.

Speechmaking

Stand up to be seen, speak up to be heard, and sit down to be appreciated.—Anon.

The Voyage of Life

In the midst of the current of life was the Gulf of INTEMPERANCE, a dreadful whirlpool, interspersed with rocks, of which the pointed crags were concealed under water, and the tops covered with herbage, on which EASE spread couches of repose, and with shades where PLEASURE warbled the song of invitation. Within sight of these rocks all who sailed on the ocean of life must necessarily pass. REASON, indeed, was always at hand to steer the passengers through a narrow outlet by which they might escape; but very few could, by her entreaties or remonstrances, be induced to put the rudder into her hand, without stipulating that she should approach so near unto the rocks of PLEASURE that they might solace themselves with a short enjoyment of that delicious region, after which they always determined to pursue their course without any other deviation.

REASON was too often prevailed upon so far by these promises, as to venture her charge within the eddy of the Gulf of INTEMPERANCE, where, indeed, the circumvolution was weak, but yet interrupted the course of the vessel, and drew it, by insensible rotations, towards the center. . . . Those few whom REASON was able to extricate generally suffered so many shocks upon the points which shot out from the rocks of PLEASURE, that they were unable to continue their course with the same strength and facility as before, but floated along trimorously and feebly, endangered by every breeze, and shattered by every ruffle of the water, 'till they sunk, by slow degrees, after long struggles and innumerable expedients, always repining at their own folly, and warning others against the first approach of the Gulf of INTEMPERANCE.

But such as had often fallen against the rocks of PLEASURE commonly subsided by sensible degrees, contended long with the encroaching waters, and harassed themselves by labors that scarce HOPE herself could flatter with success.

As I was looking upon the various fate of the multitude about me, I was suddenly alarmed with an admonition from some unknown Power, "Gaze not idly upon others when thou thyself art sinking!" I looked, and, seeing the Gulf of INTEMPERANCE before me, started and awaked.*

*Samuel Johnson (1709-1784)

Cover Photo

The University of Sydney

The picture shows the front facade of the main buildings of the University of Sydney. They were commenced in 1854 and completed in 1859. The architect was Edmund Blacket who designed many handsome buildings of grace and fine proportion throughout the young colony.

The style is neo-Gothic and the material is sawn and picked sandstone. There is a central tower containing a fine carillon which was contributed by graduates in memory of their colleagues who lost their lives in World War I. At the rear of this view is a large enclosed quadrangle. All the buildings surrounding the quadrangle are of sandstone, and shaded, pillared cloisters enclose a central, spacious lawn. At one corner is a Great Hall in which graduation and official ceremonies are held. Its tall, vaulted roof adds to the dignity and splendour of its intricately carved walls in proportions that are similar to Westminster Hall.

Inborn Errors of Folic Acid Metabolism

Regulation of the Interconversion of Active Derivatives of Folic Acid

P. B. ROWE, M.B., B.S., M.R.A.C.P.*

EXTENSIVE RESEARCH has been undertaken during the past 30 years into the chemistry and biological activity of the essential human dietary requirement, folic acid, its reduced derivatives, and their various substituted derivatives and analogues.[2,10]

The description of a number of inborn errors of folate metabolism[1] has, however, highlighted the deficiencies in our knowledge of mammalian folate metabolic pathways. Accordingly, we have undertaken a series of studies relating to the enzymes involved in the reduction of folic acid to its active metabolite tetrahydrofolic acid and the subsequent synthesis and interconversion of the one-carbon carrier derivatives of tetrahydrofolate.

Our studies to this point have been concerned with evaluating first, the potential enzymatic activities of different enzymes in the folate pathway, in order to obtain an estimate of the relative flux of metabolites through branches of the pathway, and second, possible regulatory mechanisms which must be involved in controlling the activities of different enzymes in a complex series of interconversions.

The Mammalian Folate Pathway

Figure 1 summarizes the knowledge to date of normal folate metabolism in the mammal. Dietary folic acid polyglutamates are split in varying degrees into their oligoglutamate derivatives by γ-glutamyl carboxypeptidases ("conjugase") in the small bowel. These derivatives are actively absorbed in the small bowel. All mammalian cells appear to contain, to a varying extent, at some stage in their life cycle, the necessary enzymatic machinery to reduce folic acid to its dihydrofolic acid (DHF) and tetrahydrofolic acid (THF) derivatives and thence to the wide variety of one-carbon carrier molecules necessary for the biosynthesis of purines, pyrimidines, methionine, etc. The liver has the highest content of these enzymes, with high activities also present in rapid-turnover tissues such as the small intestine and the bone marrow.

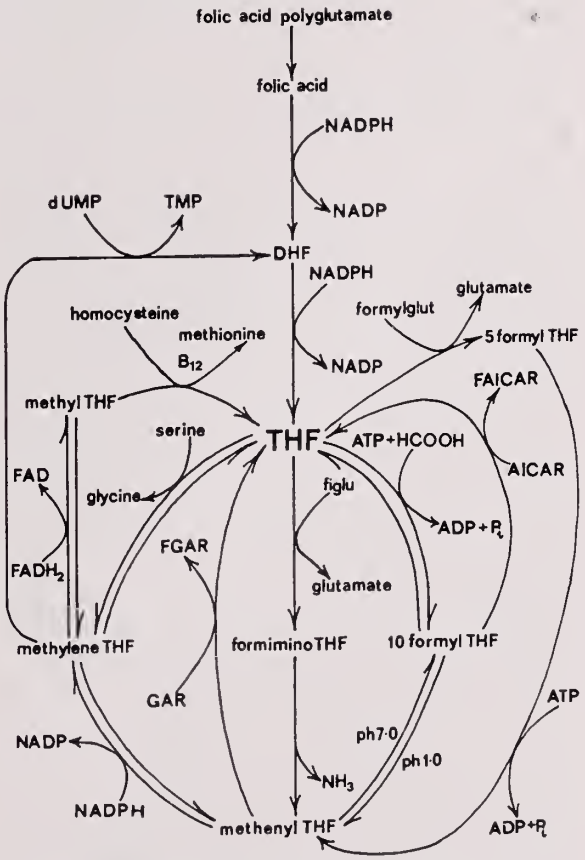


Fig. 1—Pathways of mammalian folate metabolism (Based on Blakley[2] and Stokstad and Koch[10]).

*Senior Lecturer in Child Health, From the Department of Child Health, University of Sydney.

Regulatory Mechanism in the Interconversion

At this time it appears that the major interconversion reactions in the mammal are:

1.

The reduction of folic acid to dihydrofolic acid and subsequently to tetrahydrofolic acid by reduced nicotinamide adenine dinucleotide phosphate-dependent enzymes whose activities appear to reside in the same protein molecule.

2.

The formylation of tetrahydrofolic acid to 10 formyl tetrahydrofolic acid by an adenosine triphosphate-dependent enzyme, formyl tetra hydrofolic acid synthetase (Figure 2). 10 formyl tetrahydrofolic acid is an essential for the formylation of aminoimidazole carboxamide ribonucleotide, a terminal step in purine biosynthesis.

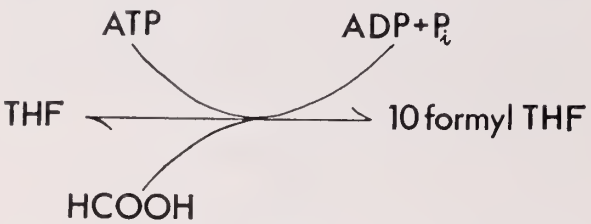


Fig. 2—Reaction catalysed by formyl THF synthetase.

3.

The generation of methenyl tetrahydrofolic acid either via the cyclization of 10 formyl tetrahydrofolic acid by the enzyme cyclohydrolase (Figure 3), the nicotinamide adenine dinucleotide phosphate-dependent oxidation of methylene tetrahydrofolic acid catalysed by the appropriate dehydrogenase (Figure 4), or the forminotransferase-cyclodeaminase one-carbon salvage pathway in histidine catabolism (vide infra). This derivative is essential for the formylation of glycineamide ribonucleotide in an early step of purine biosynthesis.

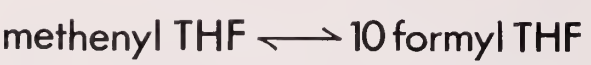


Fig. 3—The interconversion of methenyl and 10 formyl derivatives of THF by the enzyme cyclohydrolase.

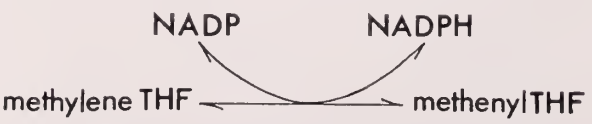


Fig. 4—The interconversion of methylene and methenyl THF by methylene THF dehydrogenase.

4.

The transfer of a one-carbon unit from serine to tetrahydrofolic acid to form $N^{5,10}$ methylene tetrahydrofolic acid. The enzyme involved, serine hydroxy-methyltransferase, has an absolute requirement for pyridoxal phosphate (Figure 5). This derivative is required for: (a) the subsequent formation of $N^{5,10}$ methenyl tetrahydrofolic acid, (b) the methylation of deoxyardine monophosphate to thymidine monophosphate and (c) the formation of 5 methyl tetrahydrofolic acid, the one-carbon donor in the vitamin B_{12}-mediated synthesis of methionine from homocysteine.

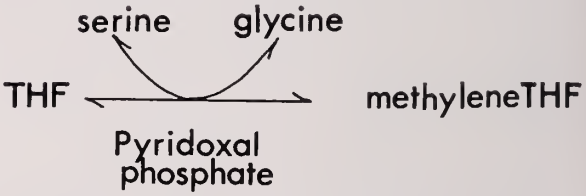


Fig. 5—The pyridoxal phosphate-dependent formation of methylene THF.

5.

The salvage of one-carbon units from histidine catabolism. Formiminoglutamic acid (figlu) is a breakdown product of histidine which forms formimino tetrahydrofolic acid via the enzyme formiminotransferase. The enzyme cyclodeaminase converts this compound to methenyl tetrahydrofolic acid (Figure 6). 5 formyl tetrahydrofolic acid, which has been isolated in significant quantities from mammalian tissue is of questionable metabolic significance. There appears to be an enzyme for its conversion to $N^{5,10}$ tetrahydrofolic acid, but its biosynthesis cannot be accounted for in terms of known pathways. Its generation from formylglutamate is, at the moment, hypothetical.

Experimental Data

We have used beef liver as the source tissue for our studies because first, all the enzymes in the pathways are present in large quantities, and second, there is reasonably close correlation between the bovine and human enzymes studied. It must be pointed out that we have been concerned only with the cytoplasmic enzymes, although small quantities of certain enzymes such as serine hydroxy-methyl-transferase appear to be present in the mitochondria.

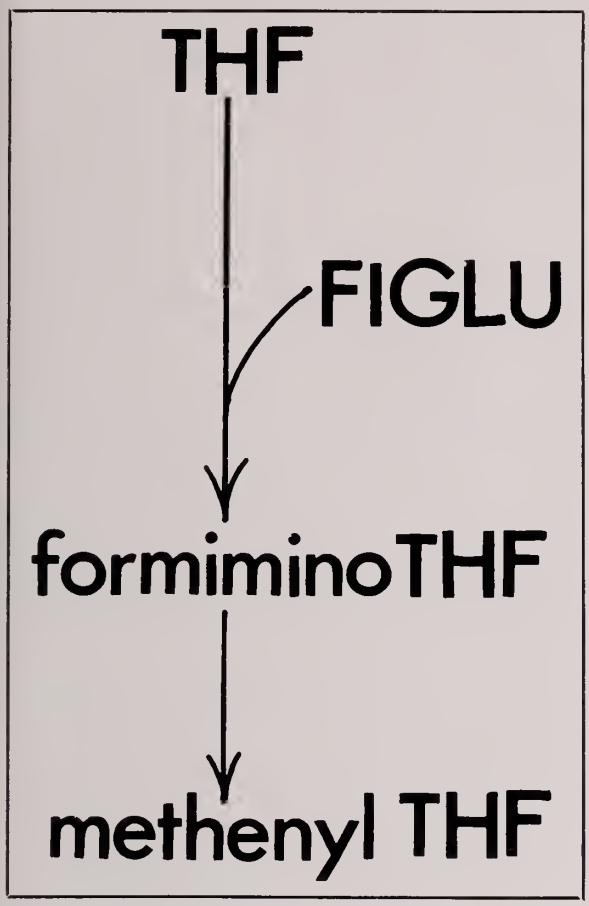


Fig. 6—The figlu salvage pathway.

Relative Enzyme Activities

The activities of folate and dihydrofolate reductase were measured in the 50-80% ammonium sulfate fraction of the 105,000 g supernatant solution of beef liver homogenate according to standard assay methods.[5]

The activities of serine hydroxy-methyltransferase,[7] formyl tetrahydrofolic acid synthetase,[9] N $^{5\ 10}$ methylene tetrahydrofolic acid dehydrogenase,[3] cyclohydrolase,[11] tetrahydrofolic acid formiminotransferase[11] and formimino tetrahydrofolic acid cyclodeaminase[11] were measured in the 0-50% ammonium sulfate fraction of the 105,000 g supernatant solution of a fresh beef liver homogenate.

Figure 7 illustrates the relative potential enzymatic activities for each step in the central part of the pathway in terms of nanomoles of substrate utilised per minute per mg protein The reduction of folic acid to dihydrofolic acid is essentially rate-limiting. The major flux of tetrahydrofolic acid is potentially its formylation to 10 formyl tetrahydrofolic acid with a high potential equilibration rate with the methenyl derivative via the cyclohydrolase reaction.

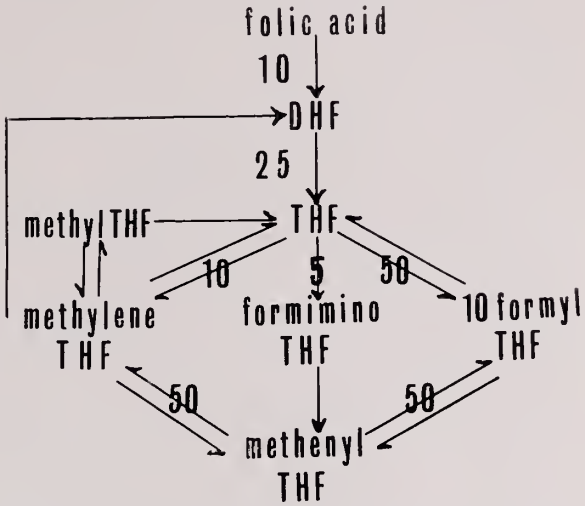


Fig. 7—The relative enzymatic activities of different enzymes of folate metabolism. The numbers indicate nanomoles substrate utilized per min. per mg. protein.

The direct conversion of tetrahydrofolic acid to N $^{5\ 10}$ methylene tetrahydrofolic acid is of relatively low activity, as is the conversion of tetrahydrofolic acid to methenyl N $^{5\ 10}$ tetrahydrofolic acid via formimino tetrahydrofolic acid. This latter pathway is assessed by an assay which measures both enzymes together, but subsequent studies indicated an approximate 2:1 ratio for the activity of the first enzyme compared with the second.[8] There is a large potential activity for the N $^{5\ 10}$ methylene tetrahydrofolic acid dehydrogenase, the equilibrium for this reaction lying towards the formation of methenyl N $^{5\ 10}$ tetrahydrofolic acid.

No activity values have been accurately measured as yet for the methylation of deoxyuridine monophosphate and the reduction of methylene to methyl tetrahydrofolic acid, but they appear to be low compared with the serine hydroxymethyltransferase reaction.

Regulatory Mechanisms of Individual Enzymes

In order to evaluate possible regulatory mechanisms for the involved enzymes, each individual enzyme was first purified and then examined for possible regulation by the various metabolites involved in the pathway as listed in Figure 8. Of the enzymes examined to this point the following are regulated by related metabolites, folate and dihydrofolic acid reductase, N $^{5\ 10}$ methylene tetrahydrofolic acid

dehydrogenase, formimino tetrahydrofolic acid cyclodeaminase, formyl tetrahydrofolic acid synthetase and cyclohydrolase. No regulatory mechanisms have been demonstrated for formiminotransferase or serine hydroxymethyltransferase.

Formate	THF
Serine	Methylene THF
Glycine	Methenyl THF
Methionine	Methyl THF
Homocysteine	10 formyl THF
Formiminoglutamate	5 formyl THF
dUMP	ATP, ADP, AMP
T M P	NAD, NADP, etc.

Fig. 8—Intermediates of folic acid metabolism assessed as potential regulators of the enzymes of the pathway.

Folic + dihydrofolic acid Reductase

This enzyme was purified according to the technique of Kaufman and Gardiner.[5] As in other species the bovine protein of molecular weight approximately 25,000 contained both reductase activities. This enzyme is subject to substrate inhibition and is also inhibited by various derivatives of tetrahydrofolic acid. The kinetics for inhibition are still incomplete but appear to be competitive in type; 5 formyl, 10 formyl, methylene and methenyl derivatives all inhibit the enzyme strongly, while 5 methyl appears to be a milder inhibitor. $N^{5\,10}$ methenyl tetrahydrofolic acid is a highly potent inhibitor with a Ki of the order of 5.10^{-7}M.

Methylene Dehydrogenase

This enzyme was purified according to the method of Dalal and Gots.[3] Tetrahydrofolic acid, 5 methyl, 10 formyl and 5 formyl were all, to varying degrees, apparent non-competitive inhibitors with respect to the substrate $N^{5\,10}$ methylene tetrahydrofolic acid. Figure 9 is a Lineweaver-Burke plot of the activity of the enzyme in terms of its substrate, $N^{5\,10}$ methylene tetrahydrofolic acid, and the inhibitor tetrahydrofolic acid. Adenosine triphosphate (ATP) and other purine ribonucleoside triphosphates, which were potent inhibitors of this enzyme from Salmonella typhimurium,[3] had no effect whatsoever on the beef liver enzyme at any stage of its purification.

Formyl Tetrahydrofolic Acid Synthetase

The activity of this enzyme, purified according to Rabinowitz and Pricer,[9] which catalyses a highly reversible reaction, is modulated by the ATP/ADP ratio, ADP being a competitive inhibitor of ATP in the forward reaction (Figure 10).

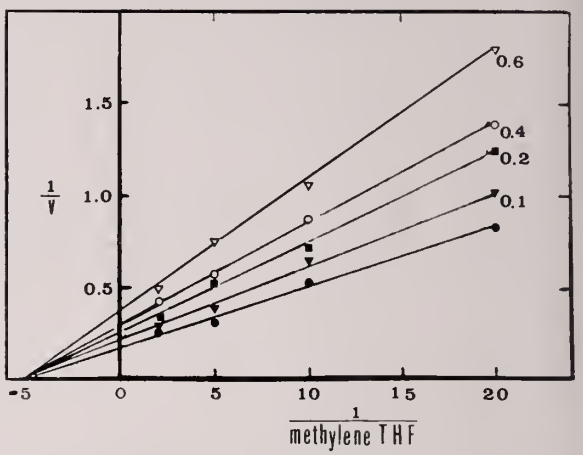


Fig. 9—Lineweaver-Burke plot of the kinetics of inhibition of methylene THF dehydrogenase by THF. The numbers on the inhibitor plots indicate the concentration of THF in m.moles. Methylene THF concentration is also millimolar.

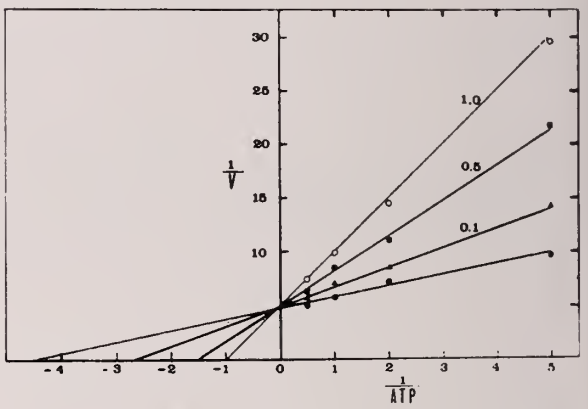


Fig. 10—Lineweaver-Burke plot of the inhibition of formyl THF synthetase by ADP. Numbers on the plot indicate ADP concentrations. Both ADP and ATP concentrations are millimolar.

Formimino Tetrahydrofolic Acid Cyclodeaminase

The rate-limiting reaction in the relatively minor salvage pathway is the second one, the cyclodeaminase reaction. The enzyme was partially purified according to Tabor and Wyngarden[11] and its inhibition by tetrahydrofolic acid demonstrated. This confirmed an earlier observation on the pig liver enzyme.[11]

Cyclohydrolase

The activity of this enzyme is inhibited by folic acid, dihydro and tetrahydro folic acid and its derivatives. Methylene tetrahydrofolic acid is a particularly potent inhibitor with akc of the same order as the km for methylene

THF.

Discussion

The demonstration by Arakawa and his associates of three closely related inherited metabolic disorders resulting from disturbances in the enzymic interconversion of *tetrahydrofolic acid* derivatives emphasised our lack of understanding of this metabolic pathway.

These conditions all manifested three primary features of mental retardation, marked elevation of serum folate levels and a deficiency of one of the folate pathway enzymes (Figure 11). The mental retardation is associated with microcephaly, cerebral atrophy (or failure of cerebral development) with dilatation of the cerebral ventricles. It is not known to what extent folate and its derivatives each contributes to the marked elevation in serum folate levels. The enzymatic defects—and these were a relative rather than an absolute deficiency of the enzyme involved in each condition—were (Figure 12): 1. cyclohydrolase deficiency; 2. formiminotransferase deficiency (perhaps with associated cyclodeaminase deficiency), and 3. homocysteine methionine methyltransferase deficiency.

Congenital disorders of THF metabolism

1. Mental retardation.
2. Grossly elevated serum folate.
3. Deficiency of an enzyme associated with interconversion of THF derivatives.

Fig. 11—Cardinal features of inborn errors of folate metabolism.

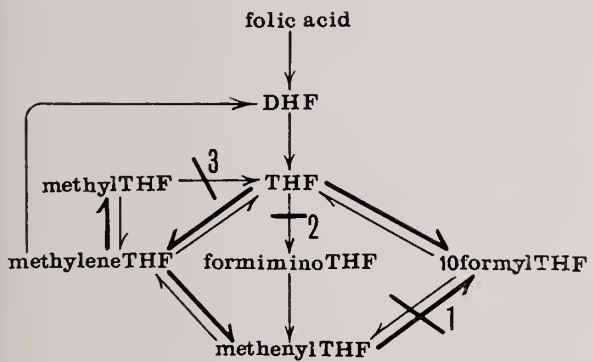


Fig. 12—Sites of partial enzymatic deficiency in the inborn errors of folate metabolism. 1. Cyclohydrolase deficiency. 2. Formiminotransferase deficiency. 3. Homocysteine-methione methyltransferase deficiency.

It must be emphasised that the method of assay used in the studies on these cases would not reveal any disturbance in kinetic constants for the affected enzymes, as all measurements were made under conditions of substrate saturation. This could be of critical importance under conditions where the substrate became limiting.

If indeed the flux across the different branches of the pathway is similar in human and in beef liver, then it is difficult to understand how relative deficiencies of enzymes 1 and 2 could lead to a limitation of supply of one-carbon donors when the site of the block can be readily bypassed. The only situation where this could arise is when absolutely maximal operation of the biosynthetic pathways is required, under which condition less than optimal supply of these compounds could be achieved. The position with respect to the third defect is somewhat different, as methionine biosynthesis is directly involved. The clinical picture, however, is very similar.

It is clear, nevertheless, that the various derivatives of folic acid are potent regulators of the enzymes involved in their own synthesis. The relative flux through different branches of the folate pathway is determined by the relative concentrations of these different derivatives. With these controls in mind, a suitable mechanistic hypothesis can be proposed for the metabolic defect arising from deficiencies of each of the enzymes involved.

When cyclohydrolase activity is lowered there is a relative accumulation of 10 formyl *tetrahydrofolic acid* and a decrease in the cyclization to $N^{5\,10}$ *methenyl tetrahydrofolic acid*. This will tend to reverse the formylation reaction; *tetrahydrofolic acid* levels will be elevated and *tetrahydrofolic acid* preferentially directed into the lower flux branches of the pathway. The relative accumulation of *tetrahydrofolic acid* and 10 formyl *tetrahydrofolic acid* will tend to shut down the further production of *tetrahydrofolic acid* from folate. Additionally, the production of $N^{5\,10}$ *methenyl tetrahydrofolic acid* will be lowered by *tetrahydrofolic acid* inhibition of both methylene dehydrogenase and cyclodeaminase and by 10 formyl *tetrahydrofolic acid* inhibition of methylene dehydrogenase. The metabolic problem then resolves itself into a question of the relative availability of key metabolites during a critical period of growth. If the enzyme were completely absent, then the individual probably would not survive; but with limited activity present, a defective individual survives.

A deficiency of homocysteine—methionine methyltransferase activity would result in a situation biochemically analogous to that of vitamin B_{12} deficiency. Apart from a failure of methionine biosynthesis, the accumulation of 5 methyl *tetrahydrofolic acid* would result in inhibition of folate and dihydrofolate reduction as well as inhibition of the methylene dehydrogenase enzyme. Once again it must be appreciated that the situation is a dynamic one with the metabolic defect resulting from a *relative* lack of key metabolites.

With formiminotransferase deficiency, an explanation is not as readily proposed, as this is a relatively low-flux salvage pathway. Figlu accumulation does not affect any of the pathway enzymes and it seems unlikely that any of the other histidine catabolites would produce inhibition. Under conditions of rapid growth, however, when other branches of the pathway were operating maximally, a defect in formiminotransferase would result in the net accumulation of *tetrahydrofolic acid* which would then shut down its own rate of production with the consequent limitation of supply of one-carbon carrier molecules.

It must be appreciated that the explanations proposed are based on dynamic principles, that is, a limitation of the supply rate of biosynthetic precursors at a period of critical growth. No provision has been made for disturbances in, for example, transport mechanisms for folic and its derivatives under conditions when the relative equilibrium concentrations of these different derivatives has been disturbed. The mechanisms of enzymatic regulation, however, do provide a possible explanation for the similarity in the over-all clinical picture seen with the different enzyme defects; i.e., there is in all cases a limitation of supply of one-carbon donor molecules.

It is of interest that 6 mercaptopurine, when injected into pregnant rats can produce a pathological picture in the offspring similar to that seen in these inherited metabolic disorders.[1] A wide range of birth defects including those discussed here can be produced by treatment of the pregnant animal with potent inhibitors of folic and *dihydrofolic acid* reductase, aminopterin and amethopterin.[6] The range and degree of the defects produced by these antimetabolites depend on the dose administered and the time of administration.

Studies of the type described emphasize once again that the knowledge of the basic mechanisms of most of the inherited and acquired disorders is limited by our lack of knowledge of mammalian biology. It is becoming increasingly clear that many disorders are the result of subtle changes in protein structure and function with consequent far-reaching effects, these effects being amplified by the necessary critical interaction of closely related metabolic pathways.

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High Blood Pressure

Somebody dies every month. And it was never a wizened old walnut, like John Elderkin, it was always some sound healthy man. No excuse for it. When he asked his friends at the club to explain it, he never got a clear answer. All they could talk of down there was blood pressure.*

*Clarence Day, Jr., Life With Father

Purine and Pyrimidine Biosynthesis

Allopurinol and Inborn Errors

R. M. FOX, M.B., M.R.A.C.P.* and W. J. O'SULLIVAN, Ph.D.†

CONSIDERABLE INTEREST in human biochemistry and its application to disease processes has focussed on an understanding of the sequence of enzyme reactions in a metabolic pathway. While many of these steps are well known, our concepts of the integration of these pathways and the control of genetic transcriptional and translational processes in the synthesis of the enzymes concerned are fragmentary.

Much of our knowledge has been extrapolated from conclusions drawn from the study of micro-organisms, exploiting the ease of genetic manipulation of the virus, bacteria and bacteriophage. More recently, it has been possible to apply similar approaches to human genetics, through establishment of the techniques of tissue culture and the study of biochemical disturbances resulting from mutation —the "inborn errors of metabolism." The development of pharmacological agents acting as metabolic analogs have complemented such investigations.

We are currently studying aspects of inborn errors in the purine and pyrimidine biosynthetic pathways. These disorders of nucleotide synthesis represent genetic defects in the actual synthesis of genetic material.[1]

We have been particularly concerned with hereditary orotic aciduria and the Lesch-Nyhan syndrome. During the course of our studies it was found that the administration of Allopurinol, a hypoxanthine analog used in the control of hyperuricemia, interfered with the *de novo* pyrimidine synthesis at a similar level in the pathway as the genetic defect in orotic aciduria.

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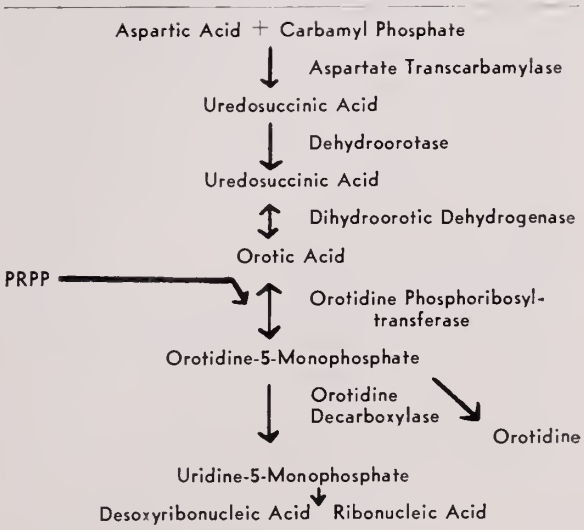
We discuss below our findings in these two conditions and some results of studies on the influence of Allopurinol on pyrimidine biosynthesis in man.

Hereditary Orotic Aciduria

In this inborn error of pyrimidine synthesis, patients have been found in infancy with a resistant megaloblastic anemia, failure to thrive, and excretion of excess orotic acid in their urine. The metabolic defect in this disorder was elucidated by L. H. Smith and his colleagues, who demonstrated a block in the conversion of orotic acid to *uridine-5-monophosphate* (UMP) due to sequential deficiency of the enzymes *orotidylic phosphoribosyltransferase* (OPrase) and *orotidylic decarboxylase* (ODcase) (Table).[1] This is a

TABLE

De-Novo Uridine-5-Monophosphate Synthesis



TABLE

defect in the *de novo* pyrimidine synthetic pathway, and the condition is transmitted as an autosomal recessive. The heterozygotes have reduced levels of both OPrase and ODcase activities and also excrete increased amounts of orotic acid in the urine.[1]

The Lesch-Nyhan Syndrome

A somewhat analogous disorder was described by Lesch and Nyhan in 1964.[2] Young males were found to have uric aciduria, mental retardation and a bizarre neurological syndrome consisting of spasticity, choreoathetosis and self-mutilation. After the demonstration that Azathioprine failed to control excessive *de novo* purine synthesis in these patients, it was demonstrated by Seegmiller and his group in 1967 that these patients have a virtually complete deficiency of the purine salvage enzyme, hypoxanthine-guanosine phosphoribosyltransferase (HGPrase).[3] This anomaly is transmitted as a sex-linked phenomenon; and tissue culture of fibroblasts from heterozygotes has revealed a mosaicism for the HGPrase as expected on the basis of the Lyon hypothesis. Partial deficiency of HGPrase has now been reported in several families in which males have been found to have gout.[4]

Present Studies

Hereditary Orotic Aciduria

We are currently investigating a family in which a variant (type II) from the classical form of hereditary orotic aciduria (type I) has occurred.* In western New South Wales, a young male infant was seen with failure to thrive and resistant megaloblastic anemia. He was found to excrete excessive amounts of orotic acid in his urine and also orotidine. Administration of uridine resulted in hematological remission. Examination of a red cell lysate soon after commencing replacement therapy revealed a virtually complete deficiency of ODcase activity. However, his OPrase activity was unexpectedly raised.[5] This was at variance with the previously reported cases of orotic aciduria where both enzymes were reduced to, or were below, the 1% level. Subsequent assays have revealed a progressive fall in the level of his red cell OPrase; and two years after commencement of uridine therapy his OPrase was at 12% of normal levels. His mother had reduced activities of both OPrase and ODcase activities (25% of normal levels), as has been found in classical or type I heterozygotes. However, she was at variance in that she was found to excrete excess orotidine (the dephosphorylated product of *orotidine-5-monophosphate* (OMP) (Table)), as well as orotic acid in her urine. Presumably *in vivo* the site of her metabolic block was at the level of ODcase. Type I heterozygotes do not excrete excess orotidine and their block is apparently at the OPrase level.

Effect of Allopurinol

Fortuitously, work in our laboratory[6] and by Kelley and Beardmore at Duke University, North Carolina,[7] has recently revealed that the administration of Allopurinol results in an inhibition of *de novo* pyrimidine synthesis which appears to reproduce the defect described above in the subject heterozygous for hereditary orotic aciduria, type II.

It has been shown that within a few days of commencing Allopurinol therapy, patients begin to excrete excessive amounts of orotidine in their urine. Normal volunteers receiving the drug (300 mg/day) excreted 30 to 69 mg/day of orotidine and somewhat lesser amounts of orotic acid. This phenomenon has also been reproduced in rats given the drug. Patients observed after several years of continued therapy still continue to excrete excess orotidine and orotic acid in their urine, while other patients, especially those with renal insufficiency, may excrete up to 400 mg/day. Normally, 1-2 mg of orotic acid and 2-3 mg of orotidine are excreted daily in the urine, although the turnover of orotic acid is about 600 mg in 24 hrs.[1]

The excess excretion of orotidine in the urine after administration of Allopurinol suggests interference with the conversion of *orotidine-5-monophosphate* to uridine-5-monophosphate by ODcase (Table). We have shown that while Allopurinol itself is not an inhibitor of ODcase *in vitro*, Allopurinol ribonucleotide is a competitive inhibitor of this enzyme. Further, Kelley and Beardmore have

*This terminology is the suggestion of L. H. Smith, Department of Medicine, University of California, San Francisco.

recently shown that of the purine nucleotides tested, *adenosine monophosphate* (AMP), *guanosine monophosphate* (GMP) and *inosine monophosphate* (IMP) have little or no effect on ODcase, but that *xanthosine monophosphate* (XMP) is a competitive inhibitor of the enzyme of the same magnitude, *in vitro,* as is Allopurinol ribonucleotide. Thus either *xanthosine monophosphate* or Allopurinol ribonucleotide has been postulated as possible mediator for the orotidinuria induced by Allopurinol.[7]

Circumstantial evidence for the latter had been obtained by *in vitro* studies on the conversion of Allopurinol to its ribonucleotide by red cell hemolysates, apparently by HGprase. Although the rate of conversion of Allopurinol was only about 1-2% of the amount of *inosine monophosphate* formed from hypoxanthine, this was sufficient to inhibit the ODcase significantly.

Further information has come from studies made on three patients with the Lesch-Nyhan syndrome. These patients were deficient in HGPrase (below 1% of normal) but excreted excess orotidine and orotic acid in their urine in response to Allopurinol administration. Hemolysates from these patients failed to convert ^{14}C-Allopurinol to its ribonucleotide after incubation with phosphoribosylpyrophosphate.

Co-ordinate response of enzymes, OPrase and ODcase

Some of our studies on the activities of the enzymes OPrase and ODcase in normals and in patients receiving Allopurinol are relevant to this concept. In hemolysates we have found there is constant proportion between the activities of these two enzymes in normal individuals, and this relationship is maintained in patients receiving Allopurinol. However, the activities are elevated several-fold above the normal range in many of the patients receiving Allopurinol. This co-ordinate relationship is thus of considerable interest because of the sequential co-ordinate deficiency in hereditary orotic aciduria of OPrase and ODcase.

Discussion

These studies have demonstrated that Allopurinol administration leads to an inhibition of *uridine-5-monophosphate* synthesis similar to that found in a heterozygote of orotic aciduria (type II). Several interesting questions in relation to this phenomenon have developed. Does the Allopurinol inhibition have any clinical significance? Is the effect due to a metabolite of Allopurinol? What is the significance of the co-ordinate enzyme response of OPrase and ODcase? Are these findings relevant to our understanding of the genetic defect in orotic aciduria? We shall discuss each of these in turn.

Any deleterious effect of Allopurinol therapy through impairment of *uridine-5-monophosphate* synthesis would presumably be reflected in abnormalities in DNA and RNA synthesis. The extreme effects of such an impairment are seen in hereditary orotic aciduria where there is a profound block in *uridine-5-monophosphate* synthesis, megaloblastic anemia and growth retardation. In this latter condition the administration of uridine by-passes the metabolic block and results in hematological remission and growth recovery.[1]

There are no reports of megaloblastic anemia attributable to the administration of Allopurinol. This is not surprising in view of our findings that most patients receiving the drug excrete orotidine and orotic acid in amounts representing less than 10% of the 600 mg of orotic acid converted to *uridine-5-monophosphate* daily. On the basis of the increased activities of the enzymes OPrase and ODcase in red cells, it would appear that there has been compensation for the impairment of *uridine-5-monophosphate* synthesis brought about by Allopurinol administration. However, it is not known whether this reflects any change in the activity of these two enzymes in the liver, where presumably the bulk of the orotidine and orotic acid are produced in response to the inhibition of ODcase. The demonstrated increase in activity of ODcase and OPrase in red cells could result from either increase in synthesis of enzyme protein in the developing erythrocyte, or by processes of enzyme stabilization or activation. Neither of these processes would be mutually exclusive.

In some patients receiving Allopurinol, especially in those with renal insufficiency, there is excretion of considerably larger amounts of orotidine and orotic acid. It is in this group that one should be alerted for possible side effects. Careful hematological evaluation would

le a useful monitor. The excessive response of patients with renal insufficiency presumably reflects a dose-related phenomenon. Elion *et al.*[8] have shown that in such patients the renal clearance of oxipurinol was impaired. Oxipurinol, the product of the action of xanthine oxidase on Allopurinol, has a prolonged half-life compared to Allopurinol and is probably responsible for the therapeutic effect. Thus the renal retention of Oxipurinol may be responsible for the excessive orotidinuria found in such patients.

We have previously postulated that Allopurinol ribonucleotide, because of its *in vitro* inhibition of ODcase, could have been responsible for the *in vitro* inhibition. Subsequent studies would indicate that this may not be correct. Studies have been carried out on patients with the Lesch-Nyhan syndrome, in which formation of Allopurinol ribonucleotide (at least in red cells) could not be demonstrated. However, these patients still excreted excess orotidine and orotic acid in response to the administration of Allopurinol. As it appears reasonable to assume that the mode of inhibition of ODcase in both Lesch-Nyhan patients and those with an intact HGPrase is the same, then some other inhibitor must be involved.

An alternate possibility is that a purine intermediate accumulating after blockage of xanthine oxidase may be responsible for the orotidinuria. In view of the finding of Kelley and Beardmore[7] that *xanthosine monophosphate* is an *in vitro* inhibitor of ODcase, it is feasible that *xanthosine monophosphate* may accumulate secondary to increased levels of xanthine. This is consistent with the findings of Pomales *et al.*[9] that, in mice, Allopurinol increases the conversion of ^{14}C-xanthine into guanylic acid of DNA, presumably via formation of *xanthosine monophosphate*. Should *xanthosine monophosphate* be an *in vivo* inhibitor of ODcase, this raises the interesting possibility that it may normally play a role as a modifier of *de-novo uridine-5-monophosphate* synthesis.

An intriguing finding in our laboratory studies has been the demonstration that there is a co-ordinate relationship between the activities of OPrase and ODcase in the hemolysates of both normal individuals and patients receiving Allopurinol: an observation which may be of direct significance to the sequential enzyme deficiency seen in hereditary orotic aciduria. In considering the relationship between these two enzymes, it is relevant to discuss some aspects of the genetic control of co-ordinate activity between enzymes. From studies on microorganisms, particularly *E. coli*, Jacob and Monod[10] developed a concept of regulatory genes responsible for the control of the structural genes which code for protein synthesis. It has been demonstrated that the activities of the terminal four enzymes leading to *uridine-5-monophosphate* synthesis in *E. coli* respond co-ordinately to the administration of uracil.[11] This led to the proposal that the structural genes coding for the synthesis of these four enzymes constitute an operon. In an attempt to draw an analogy between the mammalian and microbial systems, Smith[1] proposed that the sequential enzymic defect in orotic aciduria could be due to a defect in a regulator gene. This is consistent with the findings of Wuu and Krooth,[12] which indicated that the pyrimidine pathway in man could be delineated into smaller groups of concurrently responding enzymes.

Recent evidence tends to support the view that in mammalian cells an operon type mechanism, i.e., transcriptional control, may not be important in expression of the gene.[13] It is also apparent that the physical relationship between these two enzymes in mammals differs from that in microorganisms. For example, studies on OPrase and ODcase isolated from bovine brain and calf thymus gland failed to separate the activities of the two enzymes after a 600-fold purification.[14,15] This is in contrast to the easy separation of the respective activities in microorganisms. Thus it is possible that in mammals, including man, OPrase and ODcase form a unit, i.e., an enzyme complex, explaining the co-ordinate relationship between the two enzymes. An alternate model to the regulator gene hypothesis for the genetic defect in hereditary orotic aciduria could be a structural anomaly in the enzyme complex.

The foregoing discussion has been limited to cellular processes. Consideration of the mammalian organism as a whole reveals the situation to be more complex. Krooth[16] has demonstrated that various human tissues appear to specialize in the synthesis of certain precursors of *uridine-5-monophosphate* synthesis, presum-

ably making these metabolites available to other organs. He postulated that the entry of the metabolite into the cell is the stimulus for the development of the necessary catalytic enzymes necessary to complete the metabolic sequence. It was shown that when fibroblasts from homozygotes of hereditary orotic aciduria (type I) were grown in media containing inhibitors of *uridine-5-monophosphate* synthesis, the cells develop near normal activities of ODcase and OPrase. Krooth concluded that these inhibitors acted by increasing the intracellular concentration of one or more intermediates in the *uridine-5-monophosphate* pathway which then stimulated the cell to develop increased activity of OPrase and ODcase. It was further postulated that in hereditary orotic aciduria the primary defect was the inability of the cell to maintain an adequate intracellular level of orotic acid, leading to failure to develop adequate levels of OPrase and ODcase.

The phenomenon of organ or cell specialization in the completion of a segment of a metabolic sequence has an interesting parallel in the purine biosynthetic pathway.[17] The liver appears to be the principal site of *de-novo* purine synthesis, releasing hypoxanthine and xanthine for conversion to ribonucleotides by salvage pathway mechanisms in other tissues. Murray *et al.*[17] have suggested that these may be the major source of purines available for utilization by peripheral tissues. Our finding that Allopurinol interferes with *de-novo* pyrimidine synthesis may have an interesting bearing in this regard. Thus if *xanthosine monophosphate* is an *in vivo* modifier of *uridine-5-monophosphate* synthesis, control of xanthine levels by variation in hepatic production or transport processes could play a role in purine regulation of *de-novo* pyrimidine biosynthesis.

Summary

Allopurinol, in its role as an analog of the purine base, hypoxanthine, has the unexpected effect of inducing a partial inhibition of *de-novo* pyrimidine biosynthesis in man: a phenomenon which does not appear to be deleterious. The study of the metabolic manifestations of Allopurinol in conjunction with genetic disturbances of purine and pyrimidine biosynthesis will presumably lead to an increased understanding of the control mechanisms within and between these two metabolic pathways in man.

Comments

Further work has shown that oxipurinol ribonucleotide, presumably formed by the action of OPrase, is a likely *in vivo* inhibitor of ODCase. This finding could explain the orotidinuria observed after allopurinol administration to patients with the Lesch-Nyhan syndrome.*

Acknowledgments

We would like to thank Miss D. Royse-Smith and Miss M. H. Wood for their collaboration in these studies. This work was supported by the National Health and Medical Research Council of Australia.

*Fox, R. M., Wood, M. and O'Sullivan, W. J.: J Clin Invest May, 1971 in press).

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Some folks don't go through life—they're merely shoved through it.—Henry Vance

Humanities

Small-Pox

Relating to My Childhood

As a family picnic in summer is vexatiously disturbed by a sudden storm: so the diseases of childhood fall unexpectedly on the most beautiful season of early life. And thus it happened with me. I had just purchased "Fortunatus with his Purse and Wishing hat," when I was attacked by a restlessness and fever which announced the small-pox. Inoculation with us was still considered very problematical; and, although it had already been intelligibly and urgently recommended by popular writers, the German physicians hesitated to perform an operation that seemed to forestall Nature. Speculative Englishmen, therefore, had come to the Continent, and inoculated, for a considerable fee, the children of such persons as were opulent, and free from prejudices. Still, the majority were exposed to the old disease: the infection raged through families, killed and disfigured many children; and few parents dared to avail themselves of a method, the probable efficacy of which had been abundantly confirmed by the result.

The evil now invaded our house, and attacked me with unusual severity. My whole body was sown over with spots, and my face covered; and, for several days I lay blind and in great pain. They tried the only possible alleviation, and promised me heaps of gold if I would keep quiet, and not increase the mischief by rubbing and scratching. I controlled myself, while, according to the prevailing prejudice, they kept me as warm as possible, and thus only rendered my suffering more acute. At last, after a woeful time, there fell, as it were, a mask from my face. The blotches had left no visible mark upon the skin, but the features were plainly altered. I myself was satisfied merely with seeing the light of day again, and gradually putting off my spotted skin; but others were pitiless enough to remind me often of my previous condition, especially a very lively aunt, who had formerly regarded me with idolatry, but in after-years could seldom look at me without exclaiming "The deuce, cousin, what a fright he's grown!"

I escaped neither measles nor chicken-pox, nor any other of the tormenting demons of childhood; and I was assured each time that it was a great piece of good luck that this malady was now past forever. But alas! another again threatened in the background and advanced. All these things increased my propensity to reflection; and as I had already practised myself in fortitude, in order to remove the torture of impatience, the virtues which I had heard praised in the stoics appeared to me highly worthy of imitation, and the more so, as something similar was commended by the Christian doctrine of patience.*

*Johann Wolfgang Goethe: Autobiography.

The scientists don't seem to be sure whether splitting the atom was a wise crack.
—Chilton Times-Journal

Amniotic Fluid Analysis

Determination of Foetal Age

N. D. JOOLS, M.B., B.S., M.R.C.O.G.* and W. R. JONES, Ph.D., M.R.C.O.G.†

For many years the origin and significance of amniotic fluid has excited physiological interest, but knowledge of practical use to the clinician has had only limited application. More recently, however, detailed investigation of the constituents of amniotic fluid has yielded information of practical value. It has been shown that this fluid not only cushions the foetus against trauma and provides a medium in which it can more easily develop in an even environmental temperature, but it is also the repository for foetal secretions and excretions.

Much of our interest in the constituents of amniotic fluid has stemmed from the stimulus provided by the work of D. C. A. Bevis[1] who demonstrated the value of amniotic fluid analysis in the prediction of severity of intrauterine haemolysis in rhesus iso-immunization. The subsequent widespread use of transabdominal amniocentesis in clinical practice established the safety of the procedure; and serial sampling from mid-pregnancy onwards in cases of rhesus iso-immunization provided the opportunity to measure other constituents of liquor at different stages of gestation.

It was found that certain of these measureable constituents changed in concentration progressively with advancing gestation. Because of this progression it was suggested that quantitative analysis of these constituents might provide the basis for determination of the duration of pregnancy. Subsequent studies involved the measurement of serial changes in concentration of cholesterol, urea, protein, esterase, bilirubin, creatine and creatinine. In addition, techniques for the cytological examination of amniotic fluid were established.

The present study was designed to determine the relationship to the stage of gestation of three components of liquor amnii. The study group consisted of ante-natal patients attending King George V. Memorial Hospital, Sydney, in whom the date of the last menstrual period was recalled with certainty. A total of 91 samples of amniotic fluid were obtained from 63 patients at various stages of gestation. Serial collections were made from 21 of these patients. Samples were collected either by transabdominal amniocentesis or by the introduction of a Drew Smythe catheter into the amniotic cavity at the time of induction of labor. The amniotic fluid thus obtained was analyzed for creatinine concentration, for bilirubin by spectrophotometric analysis, and for foetal squamous cells by a cytological method.

Amniotic Fluid Creatinine

This was estimated by quantitation of the red pigment alkaline creatinine picrate (Jaffe) reaction using a Technicon N 11b auto analyzer.

It was clearly shown that creatinine concentration increased progressively with the duration of the pregnancy. This correlation is depicted in Figure 1 and the results of serial estimations are shown in Table 1.

TABLE I

Serial Determinations of Amniotic Fluid Creatinine in 10 Patients (MGM%)

Patient No.	Gestation in Weeks			
	28-30	30-32	32-34	34-37
1	0.9	1.0	1.2	—
2	0.9	—	1.1	1.7
3	0.9	1.2	1.3	—
4	0.8	1.0	1.1	1.4
5	0.9	—	1.5	2.4
6	—	—	1.4	1.5
7	0.9	1.0	1.6	—
8	—	—	1.3	1.7
8	—	1.1	—	1.5
10	—	—	1.4	1.7

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†Senior lecturer, Department of Obstetrics and Gynaecology, University of Sydney.

From these results the following guides were formulated for use in construction of a foetal maturity profile (see below).

1. If the amniotic fluid creatinine level is greater than 2.0 mgm%, then the foetal age is 37 weeks or more. This was the finding in 95% of patients and is similar to that reported by Pitkin and Zwirek.[9]
2. If the creatinine is 1.5 mgm% or greater, it is usually associated with a foetal age of 34 weeks or more. This was the finding in 97% of cases in this creatinine concentration range.
3. If the creatinine is less than 1.0 mgm%, then the foetal age is less than 30 weeks. This applied in 79% of the cases studied.

A correlation between maternal serum creatinine and liquor creatinine was noted in cases in which both were performed concurrently. In one patient with idiopathic hypercalcaemia and nephrocalcinosis the amniotic fluid creatinine of 3.4 mgm% at 33 weeks corresponded to a serum creatinine of 1.9 mgm% at the time of amniocentesis (Figure 1).

Spectrophotometric Analysis for Bilirubin

The technique described by Liley[7] was followed and the 450 mμ optical density difference (expressed as an absolute value) was determined for each liquor specimen. The 450 mμ optical density difference (O.D.Δ) is a rough but consistently reproducible index of bilirubin concentration in amniotic fluid. The number of cases assessed in this way was reduced owing to exclusion of patients subsequently delivered of babies suffering from haemolytic disease of the new-born. The results demonstrated a progressive decrease in the optical density during normal pregnancy (Figure 2). In this series it was shown that the disappearance of the peak (0.00 reading) without a subsequent rise was a fairly constant finding after the 36th week. Between the 34-36th weeks the reading was usually 0.01 or higher, whereas before the 34th week the reading was in most cases greater than 0.025. These results correspond to those published by Mandelbaum *et al.*[8] but are at some variance with those of White *et al.*[12] and Theide,[10] who reported an optical density difference at 450 mμ of less than 0.01 in a significant percentage of samples obtained before the 36th week.

Cytological Examination

In spite of the report from Blystad *et al.*[3] in 1951 that the number of squamous cells in the amniotic fluid increases with progression of pregnancy little attention was paid to amniotic fluid cytology as an index of foetal maturity until 1965 when Brosens and Gordon[4] published their results correlating foetal age with the per-

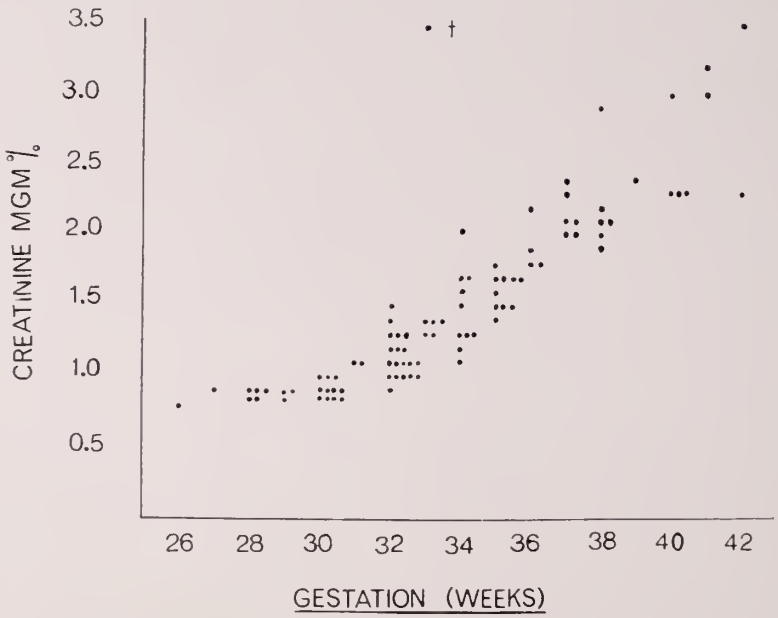


Fig. 1—Amniotic fluid creatinine concentration in pregnancy. †Patient with nephrocalcinosis and serum creatinine of 1.9 mgm%.

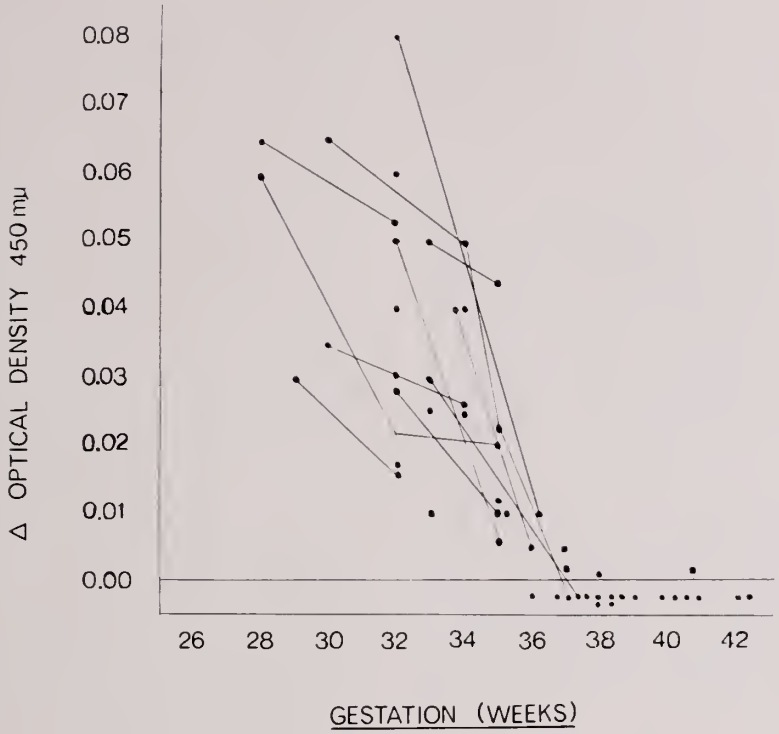


Fig. 2—Spectrophotometric analysis of liquor in pregnancy. The optical density difference at 450 mμ is plotted against gestational age. In cases with multiple determinations the values are joined.

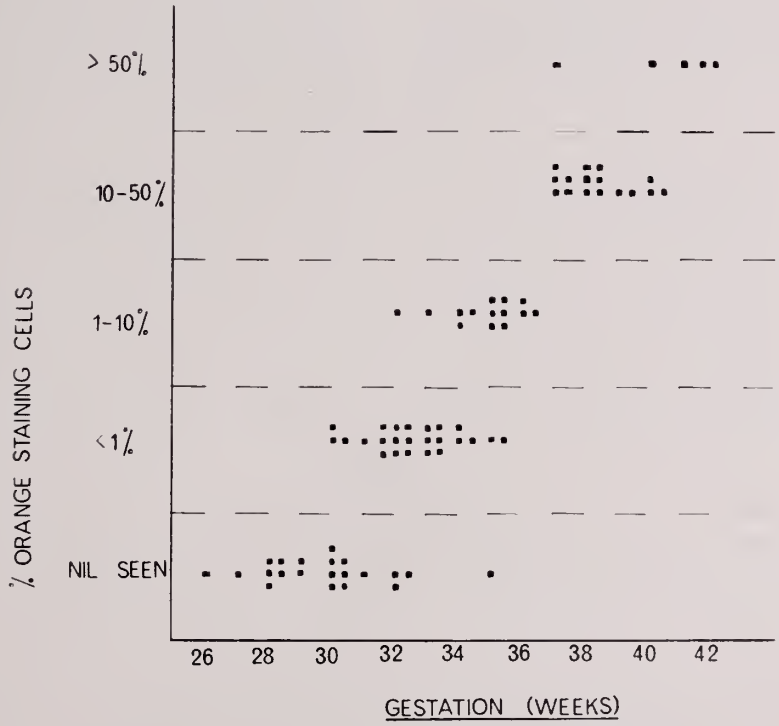


Fig. 3—Percentage of orange-staining cells in amniotic fluid throughout pregnancy.

centage of amniotic fluid cells staining orange with Nile Blue sulphate. Cells staining in this way are assumed to arise from the foetal sebaceous glands which gradually become functional with increasing foetal age.

The technique used in this study was after Brosens and Gordon[4]; one drop of liquor was mixed on a slide with one drop of a 0.1% aqueous solution of commercial Nile Blue sulphate. The slide was then gently heated at 60°C for three minutes, a cover slip applied, and the wet preparation examined microscopically to determine the percentage of orange-stained cells. Two hundred cells were counted in each sample.

Figure 3 depicts the correlation of percentage of orange-stained cells in each sample with foetal maturity. The results obtained were similar to those reported by Bishop and Corson,[2] Brosens and Gordon,[5] and Votta *et al.*[11]

A broad relationship between gestational age and percentage of orange-staining cells can be constructed as follows:

Less than 30 weeks	:	Nil
30-34 weeks	:	Less than 1%
34-38 weeks	:	1-10%
38-40 weeks	:	10-50%
Over 40 weeks	:	More than 50%

This relationship applied to 80% of the cases examined. Moreover, in all patients with a pregnancy of 38 weeks or more the cell count was greater than 10%. These results suggest that this investigation is of greater value in defining foetal maturity than either liquor creatinine or spectrophotometric analysis. In a more detailed approach to liquor cytology, Evans[6] stained amniotic fluid debris by the Papanicolaou method and determined the percentage of parabasal, intermediate, nucleated and anucleated squamous cells. He found that the parabasal and intermediate cells are gradually replaced until they disappear by 36 weeks, anucleated cells diminish after 37 weeks, and nucleated squamous cells gradually increase in number with foetal maturity.

Foetal Maturity Profile

In an attempt to increase the accuracy of foetal age prediction using the three parameters described it seemed logical to combine them in the construction of a foetal maturity profile (Table 2). The relationship between predicted and actual foetal age using the combined methods is shown in Figure 4.

A very satisfactory correlation was obtained, and it can be concluded that amniotic fluid analysis provides a reasonably accurate means for the determination of foetal age. Increased validity may be achieved by the use of multiple serial analyses, particularly in cases where premature induction of labor is contemplated. It should also be noted that the effect on amniotic

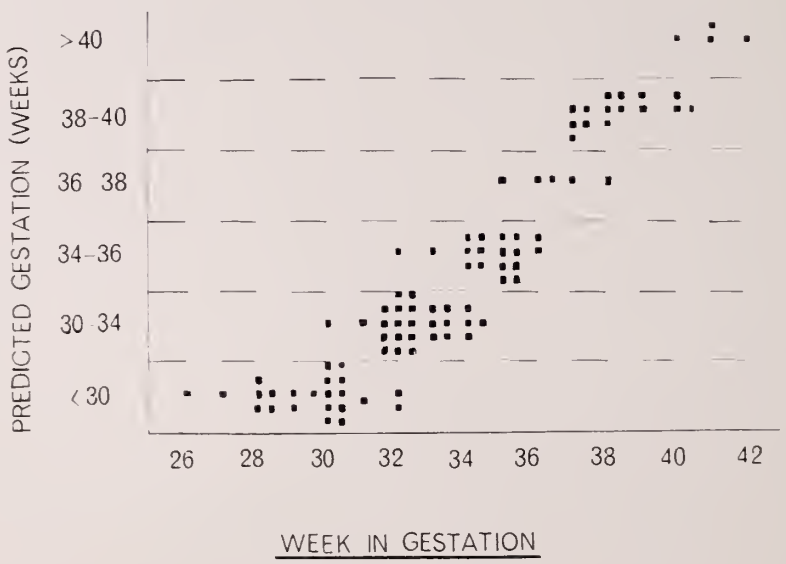


Fig. 4—Correlation between actual gestation period and predicted gestation based on a foetal maturity profile.

fluid analysis of foetal abnormalities and maternal conditions such as pre-eclamptic toxaemia and diabetes mellitis has yet to be fully evaluated.

TABLE 2

Foetal Maturity Profile Based on the 3 Parameters Studied

1. Creatinine Content mgm%	
< 1.0 mgm%	—30 weeks or less
1.5 mgm% or more	—34 weeks or greater
> 2.0 mgm%	—37 weeks or more
2. Bilirubin O.D. △ at 450 mμ.	
> 0.025	Less than 34 weeks
> 0.01	Less than 36 weeks
Nil.	Greater than 36 weeks
3. % Orange-Stained Cells in Liquor	
Nil.	Less than 30 weeks
< 1%	30-34 weeks
1-10%	34-38 weeks
10-50%	38-40 weeks
> 50%	40 weeks or more

Conclusion

The precise estimation of foetal maturity remains an unsolved problem, but recent advances have resulted in new techniques which have supplemented traditional diagnostic methods. The eliciting of a complete menstrual history, bimanual pelvic examination in the first trimester, the recording of initial foetal movements, and regular abdominal palpation provide the clinical basis for all determinations and cannot be discarded. Radiological examination using a combination of measurements and signs is a further guide in individual cases but has definite limitations.

Ultrasonic cephalometry is attaining increased usage in this field; however, like radiology it provides an indication of foetal size rather than maturity.

When there is sufficient need to define the duration of pregnancy more accurately than is possible using conventional diagnostic criteria, and when an estimate of functional rather than anatomic maturity is required, then the present study has shown that amniotic fluid analysis is a valuable additional aid. However, each patient must be individually assessed and the expected value of the information obtained weighed against the discomfort and risks (minor but not entirely insignificant) of amniocentesis.

It is concluded that amniotic fluid analysis is of value in the determination of foetal age and that a heightened degree of accuracy can be attained by combining the three parameters of creatine concentration, spectrophotometric analysis, and cytology in the formation of a foetal maturity profile.

Acknowledgments

We wish to thank Dr. C. Laverty who performed the cytological examinations and the Honorary Medical Staff of King George V. Hospital, Sydney for permission to study cases under their care.

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Run Down—Wound Up

Nearly all the people coming to a certain sanitarium for treatment were under the impression that they were completely run down. They soon learned differently. At the first weekly lecture, the doctor bluntly told them that they were all wound up, and could do little until they realized this condition and relaxed. If we periodically allow ourselves to become "run down," then Nature is given the necessary leeway to work properly in readjusting and balancing the system.*

*York Trade Compositor.

Posterior Sclerosis

"Men die of the diseases which they have studied most," remarked the surgeon, snipping off the end of a cigar with all his professional neatness and finish. "It's as if the morbid condition was an evil creature which, when it found itself closely hunted, flew at the throat of its pursuer. If you worry the microbes too much they may worry you. I've seen cases of it, and not necessarily in microbic diseases either. There was, of course, the well-known instance of Liston and the aneurysm, and a dozen others that I could mention. You couldn't have a clearer case than that of poor old Walker of St. Christopher's. Not heard of it? Well, of course, it was a little before your time, but I wonder that it should have been forgotten.

"Walker was one of the best men in Europe on nervous disease. You must have read his little book on sclerosis of the posterior columns. It's as interesting as a novel, and epoch-making in its way. He worked like a horse, did Walker—huge consulting practice—hours a day in the clinical wards—constant original investigations. And then he enjoyed himself also. *De mortuis** of course, but still it's an open secret among all who knew him. If he died at forty-five, he crammed eighty years into it. The marvel was that he could have held on so long at the pace at which he was going. But he took it beautifully when it came.

"I was his clinical assistant at the time. Walker was lecturing on locomotor ataxia to a wardful of youngsters. He was explaining that one of the early signs of the complaint was that the patient could not put his heels together with his eyes shut without staggering. As he spoke, he suited the action to the word. I don't suppose the boys noticed anything. I did, and so did he, though he finished his lecture without a sign.

"When it was over he came into my room and lit a cigarette.

" 'Just run over my reflexes, Smith,' said he.

"There was hardly a trace of them left. I tapped away at his knee tendon and might as well have tried to get a jerk out of that sofa-cushion. He stood with his eyes shut again, and he swayed like a bush in the wind.

" 'So,' said he, 'it was not intercostal neuralgia after all.'

"It took five years to kill him, and he stood it well. If he had ever been a little irregular he atoned for it with that long martyrdom. He kept an admirable record of his own symptoms, and worked out the eye changes more fully than has ever been done. When the ptosis got very bad he would hold his eyelid up with one hand while he wrote. Then, when he could not coordinate his hand to write, he dictated to his nurse. So died, in the odour of science, James Walker, at 45."†

*De mortuis nil nisi bonum—of the dead say nothing unless it is good.
†Sir Arthur Conan Doyle (1859-1930) as quoted in A. C. Corcoran: A Mirror up to Medicine, 1961.

Bigamy

Bigamy is having one wife too many. Monogamy is the same.—Anon.

Physiological Determinants

in Champion Athletes and Swimmers

A. S. REBUCK, M.B., B.S., M.R.A.C.P.*

CONTROL OF VENTILATION is largely a function of the sensitivity of the central respiratory receptors in the medulla. The main stimulus to this center is carbon dioxide, and response can be measured as minute ventilation. To test the sensitivity of the central receptors, the ventilatory response to increasing *carbon dioxide* tension can be used, and such testing has revealed some remarkable findings in champion athletes.

We have used a rebreathing technique to measure ventilatory response to *carbon dioxide* during recovery from asthma.[1] It was found that in patients with asthma, ventilatory response to *carbon dioxide* was impaired, but increased during recovery. Furthermore, some patients who, on clinical and spirometric grounds had recovered from their asthma, remained poorly responsive to *carbon dioxide*. In the majority of cases this was a pointer to underlying lung disease; but in one example no explanation could be found for failure to increase response. This led to the study of a further group of subjects, certain to be free from lung disease, yet with a wide range of physical abilities.

Methods

Twelve male athletes, aged from 16 to 25 years, were studied. After forced expiratory volume in one second (FEV_1) and vital capacity (VC) had been recorded, ventilatory response to *carbon dioxide* was measured during four minutes of rebreathing from a 6-litre bag, initially containing 7% carbon dioxide and 50% oxygen (Read, 1967).[2] All studies were carried out after the subjects had been sitting quietly for 10 minutes. They had undertaken no athletic performance on the day of the test. The athletes were divided into sprinters and long-distance runners on the basis of athletic performance.

Results

Details of type of athlete, forced expiratory volume, vital capacity and ventilatory response to *carbon dioxide* are shown in Table 1. Slope of ventilatory response to increasing *carbon dioxide* (expressed as $\triangle \dot{V}_E/\triangle P_{CO_2}$) has been calculated by the least squares regression method. Figure 1 shows the spirometer recordings obtained over the test period for three subjects; *carbon dioxide tension* is shown along the lower edge, and tidal volume can be judged from the scale on the left. A wide range of ventilatory response to *carbon dioxide* can be seen in these records, and this is further illustrated in Figure 2 where regressions of representative *carbon dioxide* response lines are shown; the upper line is that of a sprinter (S) and the lower line that of a long-distance

TABLE 1.
Athletes

Type of Athlete	Vital Capacity, FEV_1 and Ventilatory Response to CO_2		
	FEV_1 (L)	VC (L)	$\triangle \dot{V}_E/\triangle P_{CO_2}$
*L	3.35	3.55	0.57
*L	2.90	3.85	0.69
L	4.30	4.80	1.74
*L	4.50	4.50	1.78
*L	4.70	5.05	3.05
*M	3.40	4.15	2.89
S	4.70	4.95	1.12
*S	4.50	5.05	1.70
*S	3.60	4.05	1.71
S	4.00	4.00	2.17
*S	3.70	4.55	3.55
*S	4.60	5.05	5.61

L = long distance
S = sprinter
M = middle distance
* = 'champion' standard

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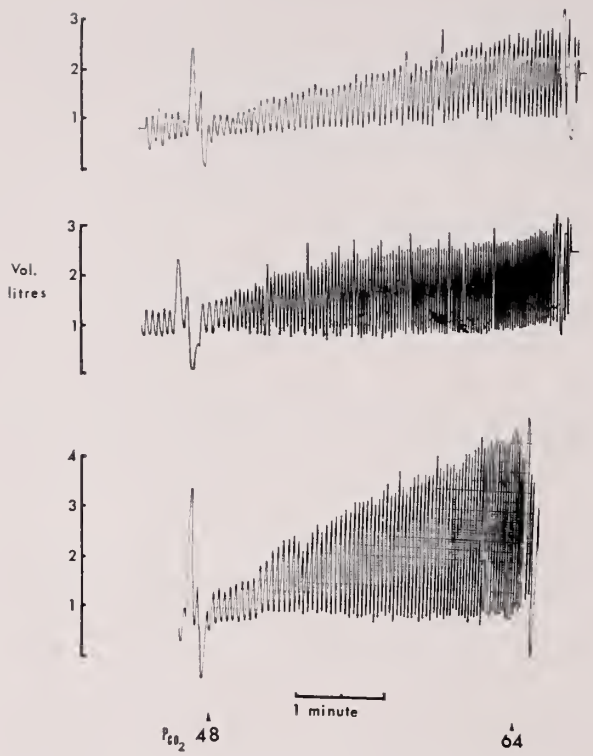


Fig. 1—Spirometer records of ventilatory response to increasing CO_2 for three subjects.

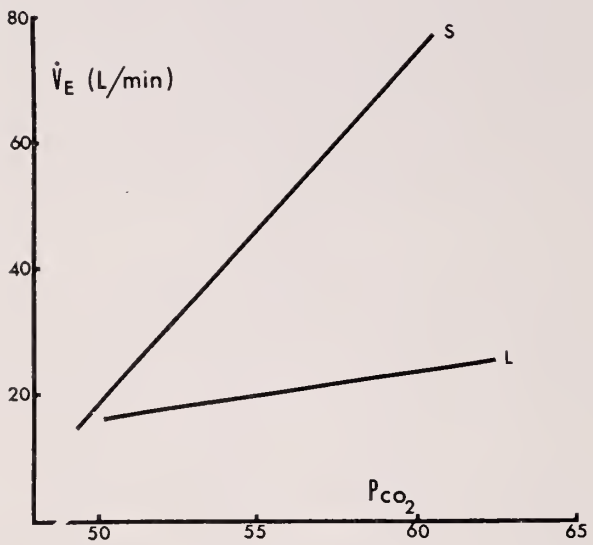


Fig. 2—Regression lines $\triangle \dot{V}_E / \triangle P_{CO_2}$ for a sprinter (S) and a long-distance athlete (L).

athlete (L).

Two subjects had slopes of ventilatory response to *carbon dioxide* of 0.57 and 0.69 litres/min/mm Hg respectively: well below any previously described for normal subjects. These athletes are current holders of Australian national records for long-distance events.

The value of 5.61 litres/min/mm Hg in subject 12, a current State sprint and hurdles champion, is well outside two standard deviations above the mean for a further 38 normal subjects studied in this laboratory (*mean = 2.68 litres/min/mm Hg. S.D. = 1.04*).

Nine of the athletes were current holders of State or Australian records or titles. Figure 3 shows part of the ventilation—*carbon dioxide tension* plot for each of the champion sprinters (dotted lines) and long-distance champions (solid lines) between *carbon dioxide tension* 55 and 65 mm Hg. The levels of ventilation at a P_{CO_2} of both 55 and 65 mm Hg were lower for the long-distance performers than for the sprinters (*$P < 0.025$ and < 0.05 respectively*).

Ventilatory Response to CO_2 in Olympic Swimmers

A major question to be answered is that of the effect of training on the low ventilatory response to *carbon dioxide* in long-distance champions. Certainly the type of training for long-distance runners is very different from that of sprinters. The study was therefore repeated in five Australian Olympic swimmers, selected at a time when they had undergone training under close supervision, swimming between five and nine miles every day for several months—endurance work by any standards.

Results are given in Table 2. Despite the uniform training program, a similar pattern to that in the athletes emerged. Two of the long-distance champions, including the current Olympic 1,500 meters bronze medallist, had slopes of $\triangle \dot{V}_E / \triangle P_{CO_2}$ below 2 litres/min/mm Hg. Two of the sprinters had slopes greater than 4.5 litres/min/mm Hg. The slope of 8.2, by far the highest ever recorded, was produced by a Mexico Olympic Games sprint medalist and is one which, if extrapolated, would mean that at *carbon dioxide tension* of 65 mm Hg he would be breathing at a rate of 184 l/min.

TABLE 2.
Swimmers

Sex and Age	Type of Swimmer	Vital Capacity, FEV_1 and Ventilatory Response to CO_2 FEV_1	VC	$\Delta \dot{V}_E / \Delta P_{CO_2}$
M 15	M	4.20	4.35	2.47
F 15	L	3.40	3.65	1.75
M 21	L	5.05	5.15	1.50
M 18	S	4.20	6.00	4.86
M 21	S	5.95	7.30	8.17

L = long distance
S = sprinter
M = middle distance

Discussion

There have been numerous studies to determine whether parameters of respiratory physiology could account for outstanding athletic performance. Linderholm[3] has suggested that diffusing capacity of the lungs is a limiting factor for physical working capacity, and it is known that champion middle-distance athletes[4] and swimmers[5] have higher diffusing capacities than normal subjects.

No studies have pinpointed any significant difference in pulmonary physiology between sprinters and long-distance champions, although Goff and Bartlett[6] have noted high end-tidal *carbon dioxide* tensions in trained underwater swimmers.

The present study indicates that the combination of slope and position of *carbon dioxide* response lines can separate subjects with outstanding sprinting ability from those with natural ability for endurance events.

It may be that in athletes the extremes of responsiveness are determined by extremes in the variety of training. However, among the swimmers, response correlated more with ability than with training. On the other hand, the innate sensitivity of the respiratory center to chemical stimuli may be a major determinant of whether a man can be a champion distance performer.

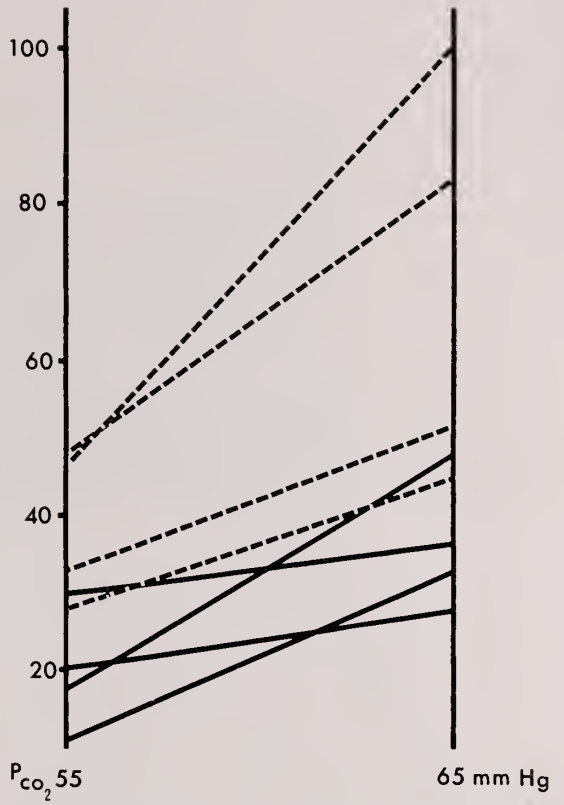


Fig. 3—Ventilation ($\dot{V}_E$) in litres per minute plotted against P_{CO_2} (mm Hg) for 8 champion athletes between P_{CO_2} of 55 and 65 mm Hg. The uninterrupted lines refer to the long-distance runners, the interrupted lines to the sprinters.

Acknowledgments

I wish to thank Mr. S. Pross (Coach of the Australian Athletic Team) and Mr. D. Talbot (Coach of the Australian Swimming Team) for their enthusiastic cooperation.

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A bare assertion is not necessarily the naked truth.—George Prentice

Historic Hospitals

The "Rum Hospital," Sydney



The original south wing of the "Rum Hospital," Sydney. Courtesy of The National Trust of Australia.

The oldest hospital building in Australia is the "Rum Hospital" at Sydney. It gains its name from the unusual financial arrangement developed by Governor Lachlan Macquarie to provide the struggling colony with a large general hospital at no expense to the government. In 1811 the governor awarded to three prominent colonists the right to import and dispose of 45,000 gallons of rum within a period of three years. In return, the three men agreed to build during the same period a building "elegant and commodious, and sufficiently large to accommodate, comfortably, at least two hundred sick persons" and also "suitable quarters for all the medical officers who may be required at Sydney." The awarding of a virtual monopoly in the rum trade embarrassed officials in London, not so much because of the unusual terms, but because the British Government had already given licenses to several persons for the export of liquor to Australia.

The ambitious project presented a challenge to the three contractors because there was no architect in the colony. By 1816, however, they completed a central building as a hospital for the free poor of the colony, a south wing for sick convicts and assistant surgeons' quarters, and a north wing providing the quarters of the principal surgeon. The hospital was too large for the colony's requirements, but stood as a monument to an enterprising governor.

In 1879 the central building was demolished to make way for Sydney Hospital. The south wing, shown above with little change in its exterior, became the Australian Mint in 1853, and is still known by that name. The north wing received some additions, and since 1829 has been the State Parliament House of New South Wales.

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Crispies or Crunchies?

"To what do you attribute your long life?" the reporter asked the man celebrating his 100th birthday. "I can't rightly say yet," the old-timer replied. "I'm still dickering with two breakfast-food companies."*

*Mark Wachs

Abnormal Illness Behaviour

The Assessment

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PATIENTS PRESENTING with physical complaints for which no adequate somatic explanation can be found constitute a considerable problem for psychiatrist and non-psychiatrist alike.[6] It is the latter, however, who is usually required to make the initial assessment of these patients, and much has been written concerning "familiar faces" and "thick folders" which bears witness to the need for clarification in this confused and difficult area.

In a previous paper[5] I have suggested that the concept of "abnormal illness behaviour" provides a useful framework within which to consider the issues raised by this group of patients. The purpose of this paper is to consider in greater detail the steps to be taken and the variables to be considered in deciding whether a patient is manifesting abnormal illness behaviour, and to suggest how one might most usefully classify the various manifestations of this behaviour.

The notion of "abnormal illness behaviour" is based on the concept of "illness behaviour" formulated by Mechanic.[1] He has depicted this phenomenon as "the way in which given symptoms may be differentially perceived, evaluated and acted (or not acted) upon by different kinds of persons." (Individuals who delay seeking help or deny illness obviously constitute an important group but will not be discussed in this paper, since their detection and management raise issues which are of a somewhat different type from those being considered in the present context.)

On this basis, "abnormal illness behaviour" may therefore be defined as the persistence of an inappropriate mode of perceiving, evaluating and acting in relation to one's state of health, despite the fact that a doctor has offered a reasonably lucid explanation of the nature of the illness and the appropriate course of management to be followed, based on a thorough medical examination (including special investigations where necessary). The patient's response to the doctor's explanation has been stressed in this definition since, in most societies, individuals are expected to consult a medical practitioner in deciding the nature of the "sick role"[3] to which they are entitled.

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The Patient's Medical Adviser

It will also be noted that as a consequence the diagnosis of this syndrome must needs depend, in large measure, on the behaviour of the patient's medical adviser. If his examination is perfunctory or his explanations vague and ambiguous, the diagnosis of abnormal illness behaviour cannot be made with any confidence. Apart from this consideration, there is also the need for the doctor's behaviour to be consistent and appropriate if he is to acquire knowledge and understanding of illness behaviour in the cultures he encounters, for it is on this sort of information that his judgment of an individual patient's illness behaviour must ultimately rest.

Physical and Personality Assessments

It is important to specify with some degree of precision what is implied by a thorough examination and an adequate explanation, as their nature is crucial to the diagnosis of abnormal illness behaviour. To be considered thorough, an examination must include an assessment of the patient's mental state and personality in addition to an appraisal of the interpersonal and environmental stresses he is experiencing. This does not imply two entirely separate examinations. Most doctors are quite capable of carrying out physical and personality assessments concurrently (and many do so without conscious awareness of their being engaged in

such an activity). If examinations are routinely done in this way, the patient is introduced to "psychological" concepts as a matter of course, and the sudden switching to a psychological wavelength after an exclusive attention to the physical is not perceived as an abrupt rejection of the symptoms which the patient has presented.

To tell a patient "I can't find anything wrong—it's your nerves—you'll have to see a psychiatrist," obviously does not constitute a proper explanation. Most patients translate this as "I don't believe you really have got your symptoms—it's all your imagination—if you can't pull your socks up and stop having these symptoms, you will have to see a psychiatrist—you're certainly not going to waste any more of my time." Unfortunately the patient's interpretation is often only too accurate, and since the complaint behaviour may constitute a reaction to feelings of rejection in the first place, it is hardly surprising that this type of response on the doctor's part frequently stimulates the patient to press his symptoms with even greater emphasis and conviction.

Comprehensive Evaluation

A comprehensive evaluation of the patient as a totality has the further advantage of permitting an appraisal of all factors which may have determined the nature and localization of his complaints. Without such an examination, a clear exposition of the situation to the patient is not only impossible, but the danger of overlooking serious organic pathology becomes much more likely.

In this regard it is probably useful to assume that a somatic sensation of some sort forms the basis for every physical complaint, even though it may be an entirely physiological phenomenon. Thus the patient may focus on a physical sensation which others would ignore (or be unaware of), such as sinus arrhythmia, occasional extrasystoles, or normal borborygmi. Similarly, the physiological correlates of anxiety or depression often constitute the somatic focus and the patient may be concerned with symptoms such as tachycardia, sweating, tremor, dryness of the mouth or constipation. It may also be possible to elucidate the psychological variables which have influenced the choice of his presenting symptom. Thus patients are more likely to be concerned over sensations in an area which has previously been involved in disease, or may be identifying with some significant person who suffered an illness in that part. Areas of the body which are "emotionally charged" are more likely to become objects of attention, as in the case of a disability for which compensation is being claimed. The doctor's history-taking efforts should include, therefore, a survey of the patient's illness history and of his contacts with illness in those who have been close to him.

The Patient's Mental State

Having considered the process involved in determining the presence of abnormal illness behaviour, the question of a more precise diagnosis arises. To achieve this, various aspects of the patient's mental state must be appraised, and these are usefully considered under a number of headings.

Ideation

The patient's thoughts about his illness may take the form of phobias, obsessions, delusions or overvalued ideas. In the case of *phobias,* he fears (with insight into the irrationality of his fear) the possibility of illnesses which may strike him down at any time: e.g., fear of "heart attacks," "strokes," etc. The patient with an *obsession* is painfully aware that his ideas on illness are illogical but, despite all his efforts, cannot drive them from his mind. *Delusions* on the other hand, are false beliefs as to the presence of disease, held with an unshakeable conviction. The patient with an *overvalued idea* is excessively preoccupied with concerns over some realistic[1] aspect of his health and does not consider his ideas illogical, although the degree of certainty encountered in delusions is absent.

In many patients it is not possible to classify their ideation precisely and, in some, its characteristics may appear to vary from time to time.

Affect

The patient's prevailing mood may be one of depression; or it may be inappropriate, hostile, flat, anxious or indifferent.

Mode of Communicating Symptoms

Symptoms may be communicated predominantly in verbal or non-verbal terms related to the nature of the symptom. The patient may simply display a paralyzed limb or a loss of vision or voice; or, in contrast, he may present endless descriptions of symptoms he experiences inside his body. It should be pointed out, however, that symptoms such as pain can on occasion be communicated in almost the same way as a visible dysfunction is displayed: i.e., with a minimum of description or elaboration of detail.

In addition to these aspects of symptom communication, symptom presentation may also be considered in terms of whether complaints are described histrionically, laconically, circumstantially, or with reluctance or hesitation.

Motivation

As a determinant of abnormal illness behaviour, the patient's motivation may be totally outside his conscious awareness, quite consciously appreciated, or on a continuum between. In every case it is necessary to know whether questions of financial compensation are involved; whether the sick role would allow the patient to avoid a patently unpleasant situation, or whether it affords an escape from the consequences of behaviour for which he might be held responsible. Information related to motivating factors which are conscious may have to be sought from others rather than from the patient himself.

Cultural and Social Class Factors

The doctor needs to be acquainted with syndromes characteristic of specific cultures which he may encounter from time to time and which can be understood only in terms of the patient's background. Social class may also play an important part in deciding whether or not a patient is able to accept psychological explanations. Manual workers in particular are less likely to accept the suggestion that their illness should be seen in psychological rather than somatic terms.

Appraisal of the patient's behaviour in terms of the headings enumerated above should make possible the formulation of a diagnosis. The value of diagnostic exercises has often been questioned; but since, in the case of abnormal illness behaviour, diagnosis has treatment implications of considerable importance, it seems useful to delineate the syndrome categories likely to be encountered.

Neurotic Abnormal Illness Behaviour

Hypochondriacal Reactions

This syndrome may take the form of an overvalued idea with marked focussing on somatic symptoms, or a phobic disorder with fear of illness. In both cases the patient spends considerable time thinking about his health. In the case of the patient who is preoccupied with symptoms, overt anxiety is usually not a prominent feature and symptoms are presented in verbal terms without any hesitation. The phobic patients are more likely to be reticent about their complaints, often apprehensive that their worst fears will be confirmed.[4] They show overt anxiety and to a considerable degree may appreciate that their concerns are excessive and inappropriate.

Conversion Reaction

In this syndrome the dysfunction is presented non-verbally and anxiety is usually absent. With regard to ideation, the patient denies any preoccupation with health or fears about illness, but simply states that all would be well if the disability were cured. In some cases, "non-displayable" symptoms such as pain may be presented in these terms and therefore constitute conversion symptoms.[2,7]

Obsessional Neurosis

Here the patient does not display a disability but is painfully preoccupied with ideas about disease which he realizes are illogical and cannot drive from his mind. Evidence of tension and anxiety are present, and the ideas may be associated with compulsive rituals such as repetitive handwashing.

Psychotic Abnormal Illness Behaviour

Psychotic Depression

In this condition the patient complains verbally although he may not do so readily. He is preoccupied with some aspect of his health and nurtures the unshakeable conviction that he has a specific disease of some particular somatic disturbance which he may describe in anatom-

ical terms. He may believe that this is an illness which represents a deserved punishment for his supposed sins. His mood is, of course, one of profound depression but, despite this, may be masked by an attitude of concern over the imagined illness. A syndrome of this sort constitutes *a serious medical emergency with a high risk of suicide*, and early diagnosis is therefore crucial.

Schizophrenia

As in psychotic depression, the patient maintains with firm conviction that he is diseased and communicates his belief verbally. However, the mood is more likely to be inappropriate or flat rather than depressive. Furthermore, the somatic delusion may be part of a wider delusional system: e.g., a belief in the presence of a damaged liver due to the beaming of radar waves on it from a distant source. The delusional matrix is often not apparent at the outset and emerges only when probed for.

Consciously Motivated Abnormal Illness Behaviour

Unlike patients in the neurotic and psychotic groups, whose primary conflict is subconscious, although they may be aware of some of the benefits which accrue from the adoption of the sick role once this has been gained, the present group includes patients who are conscious of their wish to appear ill and the purpose for this wish. Such patients include those described as "malingerers" and those with conditions such as "Munchausen syndrome" and self-mutilation.

These patients tend to deny any preoccupation with, or concern over, illness apart from the inconvenience and disability resulting from their symptoms. It is usually information from external sources that reveals the motivation for these forms of abnormal illness behaviour.

Munchausen Group

In the Munchausen syndrome group, patients eventually become known for their repeated presentations with well-rehearsed complaints of disease entities, the presence of which is not substantiated by the subsequent clinical course.

References may be secured from the author or the reprints.

Compensation Neurosis

So-called "compensation neurosis" is a special form of abnormal illness behaviour which overlaps the consciously motivated group as well as the other categories. It is particularly difficult to evaluate, as many variables operate to produce a complex situation. These factors include social and family pressures on the individual not to underplay symptoms and to claim what is regarded as his due, as well as the often nakedly ambivalent attitudes and ambiguous explanations of the medical advisors involved in a medico-legal process, whose workings are, in most centres, highly unsatisfactory and constitute an ideal breeding ground for the generation of abnormal illness behaviour.

Management

It is not the purpose of this paper to discuss management; but some general points should be made. Since abnormal illness behaviour of the type discussed in this paper refers to conditions in which patient responses are inadequately explained by the somatic pathology present, it is worth stressing that it can exist in the presence of quite definite and possibly serious pathology. Where this is the case, management should be directed at both the somatic pathology and the emotional disturbance without attempting a rigid separation of the two. Attempts to dichotomize the patient's problems in this manner rarely serve to facilitate the therapeutic process and frequently hinder it.

Summary

In this paper the concept of abnormal illness behaviour and the steps required to make the diagnosis in a clinical setting are discussed and various syndromes are delineated. It is considered possible that an approach of this sort may facilitate and simplify the early recognition of patients in this category, with consequent avoidance of expensive, time-consuming, unnecessary and often uncomfortable investigations and therapies, which have the inevitable effect of rendering far more difficult subsequent attempts to involve the patient in a treatment programme directed at his emotional problems.

Everybody is ignorant, only on different subjects.—Will Rogers

Effect of Lactic Acid Infusion in Dogs

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D. VARGA, B.Sc.‡

After half a century of lively discussions, opinions on the cardiovascular effects of metabolic acidosis are still divided. Some recent investigators, whose papers contain detailed references to earlier work, claim[1,2] that acute metabolic acidosis causes cardiovascular depression. Others[3] deny this effect or maintain[4] that it occurs only at very low pH values.

Lactic acidosis is well known to occur in shock states. In clinical shock, lactic acid plasma level was stated to be inversely proportional to prognosis[5] and, in experimental shock, lactic acid accumulation has been suggested as a major cause of irreversibility.[6] These and similar observations provide the rationale for the advocacy of the therapeutic use of buffer solutions in shock.[7] It appeared, therefore, of interest to study the consequences of lactic acid administration in otherwise healthy dogs. In previous similar attempts the aim was to produce a maximum shift in the acid-base balance, and this was achieved by using artificially ventilated animals.[2,4] However, in shocked patients with unimpaired respiratory function arterial pH may remain normal or may even increase;[8] and we decided, therefore, to study the consequences of compensated or non-acidemic lactic acidosis by using a smaller acid load in spontaneously breathing animals.

The natural isomer of lactate was used because it is utilized more easily than the racemic mixture,[9] and the control animals were given sodium lactate which is known to have no circulatory effects.[10]

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Methods

Eleven dogs weighing 25-33 kg were anesthetized with thiopentone and intubated. Cardiac catheters were passed via the femoral veins into the pulmonary artery and into the right atrium; polythene tubes were inserted into the pulmonary artery and into both foreleg veins. Hourly doses of 2 mg/kg of heparin were administered.

Oxygen saturation of the arterial and mixed venous blood was measured with a Haemoreflector (Kipp & Zonen, Delft, Holland). Hemoglobin concentration of the arterial blood was measured spectrophotometrically and samples were taken for hematocrit measurements. Arterial blood was analyzed for O_2, CO_2 tensions and pH using Radiometer microelectrodes. Expired air was collected in Douglas bags; their content was measured in a gas meter and analyzed for O_2 and CO_2 concentration in Beckman gas analyzers. Femoral and pulmonary arterial, right atrial and pulmonary arterial wedge pressures were measured with transducers and recorded on an oscillograph. Blood temperature was measured with a thermistor and monitored on an electric thermometer. Details of these techniques are described elsewhere.[11] Plasma Na and K were measured with a flame photometer, and plasma hemoglobin[12] and plasma lactate[13] were also determined.

The Fick principle was used to calculate cardiac output; arterial pH was converted into H^+ activity ($/H^+/$) and expressed in mμEq/L. Gas tensions and $/H^+/$ were corrected for blood temperature using the blood gas calcular (Radiometer, Copenhagen). Volumes, flows and resistances were expressed in the basis of 1 M^2 BSA (body surface area). Standard statistical methods were used for the evaluation of the results.

Protocol

In six dogs control measurement (period 1, 0 time) was followed by a 90-minute intravenous infusion of 6 mM/kg body weight of l-lactic acid (Sigma Chemical Co., St. Louis, Mo.) diluted to 300 ml with saline. Measurements were taken at 0.5, 1.0 and 1.5 hours (periods 2, 3, 4), and after termination of the infusion at 2.5, 4.5 and 6.0 hours (periods 5, 6, 7).

In five dogs control measurement (period 1, 0 time) was followed by a 90-minute intravenous infusion of 6 mM/kg body weight of sodium l-lactate (pH at 38°C = 7.00). Measurements were taken at the same times as in the previous group.

Results

Lactic Acid Infusion

Alveolar ventilation, pulmonary vascular resistance and lactic acid plasma level increased during the infusion of lactic acid; other parameters (including those not shown in the Table) remained unchanged. After termination of the acid infusion, cardiac output fell, systemic and pulmonary arterial resistances and alveolar ventilation increased, arterial carbon dioxide tension fell, and lactic acid plasma level returned to normal (Table, Group A).

Sodium Lactate Infusion

The only significant changes consisted of a fall in arterial hydrogen ion and an increase in plasma lactate level (Table, Group B).

Discussion

In these experiments the immediate effects of lactic acid infusion were unspectacular, and it would be logical to assume that this was due to the absence of any major shift in the arterial hydrogen ion. However, increased rate of lactic acid infusion produced intravascular thrombosis and hemolysis, and we suspect that some of the more drastic effects of acid infusion reported by earlier investigators could have been due to these and not to increased acidity. However, changes in alveolar ventilation and pulmonary vascular resistance observed during lactic acid infusion require further analysis.

In acute metabolic acidosis hydrogen ion is determined by bicarbonate ion and carbon

TABLE

Effect of Lactic Acid Infusion in Dog

Periods		1	2	3	4	5	6	7
Time, hours		0	0.5	1.0	1.5	2.5	4.5	6.0
Lactate plasma level, mEq/l	A	1.4 (0.9)	3.5* (1.6)	3.8* (1.7)	3.6* (1.7)	1.3 (0.9)	1.1 (0.9)	1.5 (1.2)
	B	0.8 (0.3)	2.1* (0.7)	2.2* (0.7)	2.1* (1.0)	1.2 (0.7)		1.5 (1.1)
Arterial /H^+/ mμEq/l	A	46 (5)	48 (6)	49 (10)	51 (13)	41 (7)	42 (8)	47 (4)
	B	44 (2)	40 (2)	36* (2)	34* (4)	36* (5)		39* (5)
Arterial pCO_2 mm Hg	A	36 (12)	32 (10)	36 (15)	35 (17)	30 (7)	28 (7)	26* (5)
	B	40 (4)	39 (3)	40 (3)	42 (1)	44 (3)		45 (6)
Cardiac output L/min/m^2 BSA	A	3.4 (1.2)	3.5 (1.1)	3.8 (0.8)	3.8 (0.6)	2.5* (0.8)	2.0* (0.5)	1.8* (0.3)
	B	3.0 (0.2)	3.4 (0.7)	3.9 (1.5)	3.5 (1.8)	2.9 (1.2)		2.7 (1.0)
Systemic art. mean pressure mm Hg	A	146 (29)	166 (31)	177 (36)	177 (41)	176 (35)	164 (29)	145 (21)
	B	172 (13)	184 (11)	184 (17)	191 (17)	173 (26)		155 (35)
Systemic art. resistance dynes-sec/cm^{-5} per m^2BSA$\times$1000	A	3.7 (1.4)	4.0 (1.1)	3.9 (1.2)	3.8 (1.2)	6.4* (2.5)	7.0* (2.6)	6.5* (1.5)
	B	4.6 (0.3)	4.4 (0.8)	4.0 (1.0)	4.4 (0.7)	5.3 (1.8)		4.9 (1.7)
Pulmon. art. resistance dynes-sec/cm^{-5} per m^2BSA $\times$ 100	A	1.5 (1.1)	3.0* (1.2)	2.8 (1.6)	2.5 (1.6)	2.7* (0.8)	4.2* (2.2)	4.9* (2.9)
	B	2.7 (0.3)	1.9 (0.6)	2.2 (1.1)	2.5 (0.9)	3.7 (1.8)		3.5 (2.1)
Alveolar ventilation L/min/m^2 BSA	A	2.2 (0.8)	3.7 (1.6)	4.2* (1.7)	3.6 (1.8)	3.9 (1.9)	4.5 (2.5)	4.1* (1.6)
	B	2.9 (1.0)	3.1 (0.7)	3.1 (0.5)	3.1 (0.7)	2.6 (0.4)		2.7 (0.4)

Groups: A = lactic acid infusion; B = sodium lactate infusion. Periods: 1 = control; 2, 3, 4 = infusion periods; 5, 6, 7 = recovery periods. Mean values and standard deviations (in brackets) are shown. * = difference from control value statistically significant ($P < .05$).

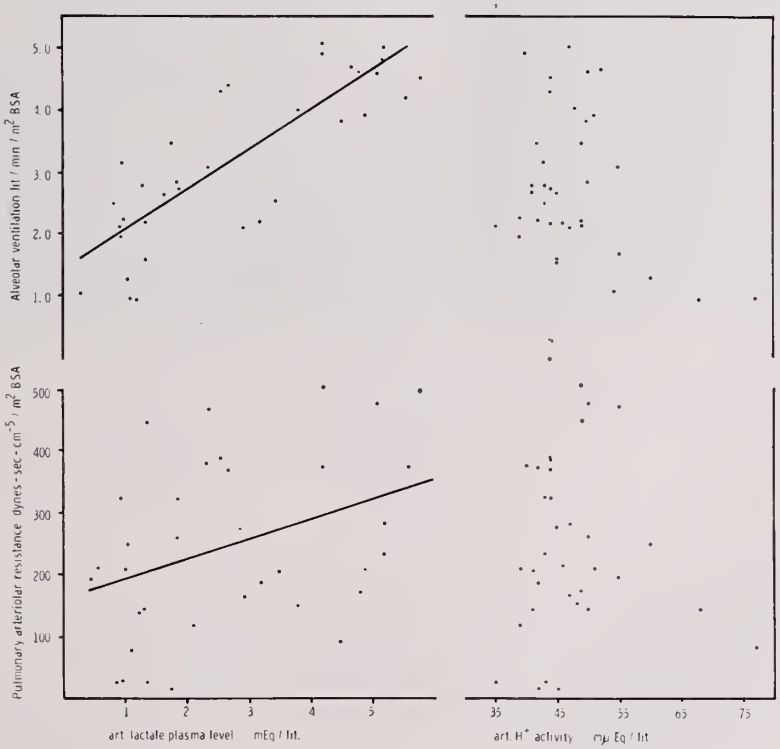
dioxide tension or, in other words, by the extent of respiratory compensation. Thus the hypothesis that H^+ represents the ventilatory stimulus is virtually untestable because, as in all closed loop systems, output (= alveolar ventilation) is determined by input (= arterial hydrogen ion) which, in turn, is regulated by output. Indeed, in such a situation constancy of arterial hydrogen ion could be considered evidence of the effectiveness of the respiratory compensation. Since the anion moiety of the lactic acid is not subject to the above limitations, change in its plasma level can be expected to be proportional to the quantity of H^+ administered. This use of lactate as a "marker" for H^+ accounts for the relationship between lactate on the one hand and, on the other hand, alveolar ventilation and pulmonary arterial resistance as shown in the Figure. However after completion of the acid infusion, alveolar ventilation remained elevated, suggesting a further increase in the ventilatory response. This delayed overshoot of the respiratory response to acute metabolic acidosis was also observed in unanesthetized dogs[14] and was interpreted to indicate a delay in cerebrospinal fluid bicarbonate readjustment.

Natural forms of metabolic acidosis are intracellular in origin and the resulting effects are likely to be related to changes in intracellular acidity. Acidosis produced by the administration of acid is primarily extracellular, and shift in the intracellular pH can be expected to follow after a time lag. We suggest, therefore, that the delayed circulatory depression seen in these experiments is the consequence of intracellular pH readjustment to prior acid infusion. It appears, therefore, that even compensated forms of metabolic acidosis may produce transient deterioration in cardiovascular function.

References may be secured from author or the reprints.

Acknowledgments

These experiments were supported by the National Heart Foundation of Australia.



Figure—alveolar ventilation and pulmonary vascular resistance related to arterial lactate level and to arterial /H^+/ during lactic acid infusion. Lines represent calculated regression. For explanation see text.

Hitting the ceiling is no way to get up in the world.—Bendixline

Laboratory Letter

A Pathologist Looks At Lithium

*"The sole indication for the use of lithium carbonate at this time is for control of manic episodes of manic depressive psychosis . . . Lithium toxicity is closely related to serum lithium levels at doses close to therapeutic levels. Facilities for prompt and accurate serum levels should be available before initiating therapy."**

IN THE CASE of lithium, the pathologist is fortunate—he doesn't have to strain his facilities (or his faculties) to measure it.

After all, lithium is simply an element. Like its univalent sisters—sodium and potassium—it can be measured accurately on a flame photometer. Serum lithium levels can be determined to within ±0.02 meq/L over a wide range of concentrations. At a maintenance serum level of 0.6-1.2 meq/L, that's an accuracy of ±1.7-3.4% and at toxic levels of 2.0 meq/L, that's within ±1.0%. But getting that close isn't necessary when you're monitoring a patient on lithium; so we report results to the nearest 0.1 meq/L.

With a flame photometer, sodium and potassium can be measured at the same sitting. This could be important since serum sodium and serum potassium have been reported to be depleted in patients on lithium carbonate.[1,2]

But lithium is prescribed as a salt, not an element. Therein lies one rub. Taken raw, it can irritate the gastric mucosa. So the manufacturers have put the salt in a gelatin capsule and colored the capsule red with erythrosine dye.

Each capsule, because it's dyed with erythrosine, contains about 190 micrograms of iodine. That amount of iodine can elevate the PBI. Which isn't necessarily bad except that patients on long-term lithium carbonate often crop up with goiters and with a low PBI. In fact, lithium may be potent goitrogen. In a recent thyroid scan study of 19 patients on long-term (17 to 126 weeks) lithium carbonate, Fieve and Platman discovered six with goiters, and four with other thyroid lesions.

If you suspect thyroid disease, then perhaps you ought to order another thyroid test, such as T-4 by Murphy-Pattee or T-3 to avoid a misleading PBI.

But that's another story for another day. On second thought, maybe life with lithium isn't going to be easy after all.

Richard L. Reece, M. D.

*FDA Current Drug Information Part of Release Statement by Federal Drug Administration, April 1970.

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Derivatively Speaking

Diaphragm—from Greek dia *(across) plus* phragm *(fence)*



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Convenience Within 4 minutes a bowl of delicious soup is heated and ready to eat.

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Contraindications: Evidence of or a history of blood dyscrasia, active organic disease of the central nervous system and the first trimester of pregnancy.

Warnings: Use with discretion during the second and third trimesters of pregnancy and restrict to patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, vomiting and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. There is no accepted proof that Flagyl is effective against other organisms and it should not be used in the treatment of other conditions. Exacerbation of moniliasis may occur.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry or sore tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Monilia,* exacerbation of vaginal moniliasis, an occasional reversible moderate leukopenia, dizziness, vertigo, drowsiness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, dryness of the mouth, vagina or vulva, vaginal burning, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, nasal congestion, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified.

Dosage and Administration: *In the Female.* One 250-mg. tablet orally three times daily for ten days. Courses may be repeated if required in especially stubborn cases; in such patients an interval of four to six weeks between courses and total and differential leukocyte counts before, during and after treatment are recommended. Vaginal inserts of 500 mg. are available for use, particularly in stubborn cases. *When the vaginal inserts are used* one 500-mg. insert is placed high in the vaginal vault each day for ten days and the oral dosage is reduced to two 250-mg. tablets daily during the ten-day course of treatment. Do not use the vaginal inserts as the sole form of therapy. *In the Male.* Prescribe Flagyl only when trichomonads are demonstrated in the urogenital tract, one 250-mg. tablet two times daily for ten days. Flagyl should be taken by both partners over the same ten-day period when it is prescribed for the male in conjunction with the treatment of his female partner.

Dosage Forms: Oral tablets . . . 250 mg.
Vaginal inserts . . 500 mg.

*References available on request.

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Editorials

International Communication in Medicine

TWENTIETH-CENTURY progress in technology has produced many changes which, on reflection, appear to be no more than mixed blessings. Thoughtful men throughout the world are constantly wondering whether the balance struck by these changes is on the positive or the negative side. In one respect, however, there is no real argument: improved communications have made it possible for men of like mind and of similar good will to make and maintain contact, to learn about each other, and to cooperate effectively.

In no area is this better shown than in modern medicine. In this field we not only have a common objective but converse together in the language of science and in the cause of humanity. Communication is especially easy between groups whose vernacular is the same and whose heritage is a common one. If there is any effective remedy for the abounding troubles that prevail in almost every area of our globe it must surely be achieved through better communication and improved mutual understanding. We in medicine, especially in the English-speaking world, are most happily placed to achieve just that. Indeed, our opportunities are so great that there is a clear onus on us to assume the responsibility.

When the Editor of MINNESOTA MEDICINE invited me, as Dean of the University of Sydney Medical School, to collect and transmit material for a special issue of his journal, the offer was accepted without any hesitation. It was subsequently learned that the Editor's brother was the U. S. Ambassador Elect to Australia and this has been a happy coincidence. We may seem far apart, but Minnesota has contributed significantly in a number of ways to medicine in Australia. Those of us with long memories will recall the visit of Charles and William Mayo to this country in 1924 when they assisted in the initial development of the Royal Australasian College of Surgeons, an organisation which has grown phenomenally and which now flourishes as the major surgical organisation of this country. Its influence is rapidly spreading throughout South East Asia, helping to bring to those areas a high standard of teaching and surgical practice. We have had many of our graduates working both in Minneapolis, Rochester and elsewhere throughout Minnesota; they have always been received with warm hospitality and assisted in their personal and professional development with generosity and kindliness. There have also been many visitors to this country from Minnesota, especially since World War II. Some of them came because they were interested in observing what was happening in a rapidly developing society; others, because they had been in Australia during the war and had enjoyed what they found. This special edition will, we hope, be yet another favorable advance in developing a bond

of mutual interest.

The University of Sydney Medical School is, by world standards, a large and quite an old one. It took its first students in March 1883, when four were enrolled. The only accommodation then available was a partly built four-room cottage in which the students set to work, although at that time the cottage lacked windows, doors and even a roof. In 1970 the Faculty consists of 1450 students and produces each year 220 to 240 graduates. The competition for entry is great. Even allowing for the large enrollment, many more applicants are rejected than accepted.

The original cottage was soon replaced by a splendid and commodious sawn-sandstone building in Tudor Perpendicular Gothic; but this, within less than 50 years, was inadequate, and a modern building was erected in 1932, funded by the Rockefeller Foundation, on the grounds that Australia was an under-developed country. That stage has passed; we have now fully emerged and finance ourselves. Since World War II development has proceeded rapidly. The full-time Faculty now contains 15 departments, and progress into newer fields is proceeding apace.

The quality of the work of the Faculty must be judged on its own merits; some indication of that quality can be acquired from the material contained in this issue. The papers were submitted by members of the Faculty with enthusiasm and pleasure, and it is hoped that they will contribute something new to the knowledge of the readers. They carry with them only good will and the earnest wish that we may be forging a small link in a growing chain of understanding and respect between our two countries.

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The Classification of Melanoma

Sir James Paget,[1] in a lecture at St. Bartholomew's Hospital in 1864, stated that the occurrence of cancer in or under pigmented moles was a well known phenomenon. Less well known, however, was the fact that pigmented lesions which give rise to melanoma can appear in adult life. It was Jonathan Hutchinson, LLD, FRS,[2] a Consulting Surgeon to the London Hospital and a former president of the Royal College of Surgeons, who brought this to public attention in his "Archives of Surgery" where we find the first description of a lesion which is often designated "Hutchinson's melanotic freckle," but which Hutchinson himself, in 1892, named "Senile freckle." He described the lesion in one of his cases (Case IV), a lady of about 60 years, as follows: "In her, the black staining is most clearly infective, for it has spread from the lower eyelid, in the skin of which it began, to the palpebral mucous membrane, and even to that of the eyeball." To Hutchinson this characteristic mode of spread was similar to an infective process. In Case V Hutchinson described "a large infective pigment patch on the cheek resembling superficial melanosis," in the margin of which a malignant nodule appeared and, though the nodule was not in the least pigmented, he had no doubt that it was of a melanotic character because of its juxtaposition with the blue-black stains.

In 1894 Hutchinson[3] reported the occurrence of a malignant nodule in the edge of the eyelid of the lady mentioned above (Case IV) and published a picture of the lesion as it was in 1892, showing the irregular pigmentation and irregular margins which characterise the lesion. He excised the malignant nodule and appended the histopathologic report by his eldest son who regarded the lesion as a melanotic sarcoma. The wound healed at once and, at the time of writing, there had been no recurrence.

Hutchinson noted the frequency of the lesion on the malar region of the elderly and how often it involves the lower eyelid. In appearance, the lesion suggests the coalescence of a number of enlarging darkly pigmented freckles, being simply a process of pigmentary staining

without appreciable thickening. "Lastly, however, another stage is assumed, and a growth takes place which is for the most part unpigmented, and which in its tendency to break down and ulcerate, reveals its malignant nature."

Hutchinson, in 1894, altered the name to *lentigomelanosis* and stated that he had also seen the lesion on the lips and on the prepuce.

The next important name in the history of this condition is Dubreuilh[4] who followed Hutchinson in calling the lesion *"lentigo malin des vieillards"* in 1894. However, he later regarded this name as unsuitable because "les lentigines" of French writers corresponds to "freckles" in English and should be kept for that purpose. Moreover, he had by this time (1912) seen lesions of similar type in young persons as well as in the elderly, his youngest patient being only 18 years old. Accordingly, he coined the descriptive phrase *mélanose circonscrite précancéreuse,* by which he meant any area of melanosis of the skin or mucosae, appearing in adult life, which in a high percentage of cases, would become malignant.

Dubreuilh reported 26 personal cases of *mélanose circonscrite précancéreuse* to which he added nine others culled from the literature. Throughout, he emphasised that apart from being acquired lesions of adult life, lesions of this type have a much greater malignant propensity than the nevi which appear in childhood. His patients ranged in age from 18 to 68 years and averaged 10 years before the onset of invasive malignancy. Lesions of the extremities, he found, became malignant after a much briefer period than lesions of the face and also were more likely to give rise to generalized metastases.

Hutchinson was primarily interested in the acquired freckle-like lesion which appears on the skin of the face of the elderly, but later he included macular lesions on the covered part of the body (prepuce, for example) which may have been present since childhood.

Dubreuilh included in the one category, lesions appearing in young people and those appearing in the elderly without distinction as to site, and also lesions of the buccal mucosa, the palm of the hand and the sole of the foot. The features they had in common were that they were areas of melanosis appearing in adult life which were likely to become malignant, and this concept is embodied in the designation *melanosis circumscripta praecancerosa* of Dubreuilh commonly used in many parts of the world. In Australia, however, it has been known for many years that this term includes two distinct lesions with differing prognoses for the melanoma arising in them. A Committee of Australian Pathologists[5] recommended in 1966 that *melanosis circumscripta praecancerosa* be divided into Hutchinson's melanotic freckle and premalignant melanosis.

Hutchinson's melanotic freckle usually appears in skin showing severe solar degeneration and is therefore most commonly seen on the face, neck, dorsa of the hands, and the forearms. It is a spreading macular lesion with an irregular outline and with variations in intensity of the pigmentation. Regression with almost complete disappearance may be followed by the appearance of the lesion nearby, a feature first reported by Dubreuilh in his Case III, in which a 49-year-old woman presented with the history that a brown melanotic freckle 3 centimetres in diameter had appeared on the nose over the previous 12 years. Over the next two years the lesion disappeared but, at the same time, a new pigmented patch appeared in the conjunctiva.

After a period up to 30 years or longer one or more nodules of invasive malignancy may appear in the lesion. These nodules are often partly or wholly unpigmented as Hutchinson first mentioned.

Premalignant melanosis (superficial spreading melanoma and pagetoid melanoma) is also a spreading macular pigmented lesion, but more circumscribed than Hutchinson's melanotic freckle and of much more uniform color. It seldom exceeds 2 to 3 centimetres in diameter and occurs on the skin of covered parts of the body and in mucosae such as that of the mouth, conjunctiva, anal region and genitalia as well as on exposed skin. Inevitably an invasive nodule appears within a few months or, exceptionally, a few years, and ulceration ensues.

Some melanomas commence without any antecedent spreading pigmented macule; instead, they invade from the beginning, arising, in the words of Dubreuilh, *"d'emblée sur une*

peau saine."

Histologically as well as clinically these lesions have distinct patterns. Hutchinson's melanotic freckle consists of a linear proliferation in the basal layer of the epidermis, seldom forming clusters unless invasion of the dermis is taking place. Both the epidermis and the dermis usually exhibit marked solar degeneration.

In premalignant melanosis there is a proliferation of melanocytes with cluster formation in the basal layer and pagetoid invasion of the epidermis prior to invasion of the dermis. Solar degeneration may be present in skin from exposed areas but is not as severe as in Hutchinson's melanotic freckle.

In the third type of melanoma, commonly called nodular melanoma, malignant melanocytes invade the dermis from the beginning.

As Clark[6] pointed out, melanoma develops in one of these three ways whether there had been an antecedent nevus or not. He[7] and his colleagues also showed that the prognosis for melanoma arising in lentigo maligna (Hutchinson's melanotic freckle) is much better than for other types of melanoma, and that melanoma arising as a nodule without any preliminary spreading melanosis has the worst prognosis.

Clark defined five levels for histological staging which also correlated well with survival.

It has been suggested in a recent Australian study[8] that there is little difference in biologic behaviour between tumours of equivalent anaplasia, the greater malignancy of nodular melanoma being ascribed to the higher proportion of very anaplastic tumours. In the Australian series there were no tumours of grade 3 anaplasia amongst the melanomas arising in Hutchinson's melanotic freckle. The significant guidelines to prognosis and management are therefore the histogenetic type of tumour, its degree of anaplasia and its depth of penetration. Other parameters which may in due course be found to have prognostic significance are the mode of growth, whether pedunculated, dome-shaped or flat, the presence of lymphocytes in the tumour, and the degree of histiocytic reaction in the regional lymph nodes.

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Another Dimension?

There was no doubt that having pneumonia had been a stupendous experience; it was almost like being outside the world altogether, or at any rate like being in a world of dream-work so terrific that I afterwards thought of it as a sort of supernatural revelation. Those vague multitudes under enormous flame-lit arches —what could they have been if they were not something to do with death? Even now I can recover my awed sensation of having been away from life, of having had a glimpse of something for which I had no words.*

*Siegfried Sassoon (1886-), English soldier and author, as quoted in A. C. Corcoran, M.D., A Mirror up to Medicine, 1961.

Inherited Spinal Muscular Atrophies

A MAJOR MOTIVATION in studying genetic disorders is to define inborn metabolic defects in terms of an altered enzyme or membrane transport process so that medical management can become more specific. However, little progress can be made with certain categories of genetic disease due to ignorance of fundamental pathways and cellular structures. Such is the case with the inherited spinal muscular atrophies. But while awaiting breakthroughs in knowledge much clarifying work can be done with available techniques.

McLeod and Williams* utilized electromyographic and histopathological findings to establish evidence of anterior horn-cell degeneration in patients who could then be distinguished on clinical grounds as having either the infantile or the juvenile form of spinal muscular atrophies. There emerged two relatively stereotyped conditions: the infantile Werdnig-Hoffmann† disease arising during the first year of life with a progressive course leading to death in early childhood, and the later onset of the Kugelberg-Welander syndrome with a variable picture but more slowly progressive. However, these stereotypes represent two oases in a vastly complicated spectrum of neurogenic disease which has generated polemics and disputes for many years. Some workers have tried to assemble each form into a few major groups; others prefer to accommodate every variant in numerous subdivisions.

There is an obvious limit to what can be achieved when only descriptive criteria are available, and at present it seems best to accept the two major varieties as base-lines. Thus, out of the heterogeneous mass that was once Oppenheim's disease and later amyotonica congenita, one can accept Werdnig-Hoffmann disease and note its major variants; arthrogryposis multiplex due to *in-utero* onset, a floppy infant presenting at birth, and, rarely, arrest of the disease during infancy or childhood. There is inevitably a merging with the Kugelberg-Welander syndrome, but, in general, the earlier the onset, the worse the prognosis.

The Kugelberg-Welander syndrome may be clinically indistinguishable from muscular dystrophy, especially in its early stages.[1] Hence the necessity for thorough neurological investigations. It is likely that some girls have been classified as suffering from Duchenne muscular dystrophy in the absence of studies which would have revealed support for the Kugelberg-Welander syndrome.[2] This kind of misdiagnosis is serious because the Duchenne variety implies almost certain death by the end of the second decade in contrast to the slowly progressive Kugelberg-Welander syndrome which sometimes causes little serious disability until middle age. Similarly, the possibility of an arrest in Werdnig-Hoffmann disease must be considered, and there is some evidence,[3] albeit disputed,[1] for a clinically identical condition, benign congenital hypotonia in which there is a slow and ultimately complete recovery.

Apart from the individual prognosis there is the genetic prognosis. Werdnig-Hoffmann disease has recessive inheritance, as have most cases of the Kugelberg-Welander syndrome. However, there are some instances of the latter syndrome with dominant inheritance.[4] Accordingly it is best to counsel families which contain the Kugelberg-Welander syndrome on the basis of recessive inheritance unless there is pedigree evidence which suggests otherwise.

The relationship of Werdnig-Hoffmann disease and the Kugelberg-Welander syndrome to other forms of spinal muscular atrophy appears a complex and, at present, insoluble problem. There are examples of the Kugelberg-Welander syndrome with features of familial bulbar palsy or corticospinal tract disease. In fact, it has been speculated that there may be a continuous spectrum of disease extending from Werdnig-Hoffmann disease at one end to adult motor neurone disease at the other.[5] Conversely, anterior horn cell disease is known to occur in other inherited neurological disorders such as Friedreich's ataxia or peroneal muscular atrophy. As McLeod and Williams concluded, we need much more information before even

*See page 457.
†See page 461.

starting to construct a rational and comprehensive classification for the genetic spinal muscular atrophies.

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Allopurinol*

VERY FEW DRUGS do only one thing, which I suppose is one reason it is better to prevent diseases than to treat them. The recent discovery (Fox, Royse-Smith and O'Sullivan, 1970; Kelley and Beardmore, 1970) that Allopurinol inhibits pyrimidine synthesis provides another example of an unexpected side-effect of a drug whose action was supposedly known. Fortunately, in this case, the side-effect appears to be without clinical significance. Nonetheless, the scientific value of this discovery is considerable.

Why should a purine, like Allopurinol, inhibit pyrimidine synthesis? The original view of Fox, Royse-Smith and O'Sullivan was that an enzyme of purine metabolism converted Allopurinol to a ribotide which in turn inhibited the final enzyme of pyrimidine synthesis. They now favor the idea that Allopurinol acts by causing an accumulation of xanthine which in turn leads to the formation of xanthine ribotide. Kelley and Beardmore (1970) have shown that this compound is also an inhibitor of the final enzyme of the pyrimidine sequence.

I prefer the first theory because it is simpler. However, Fox and his associates report in this issue of *Minnesota Medicine** that Allopurinol is not converted to its inhibitory ribotide by hemolyzates from patients with the Lesch-Nyhan syndrome—a rare sex-linked disorder. Hemolyzates of affected persons have previously been shown to have no activity for the enzyme which is likely to be responsible for converting Allopurinol to a ribotide (Seegmiller, Rosenbloom and Kelley, 1967). Yet patients with this disease, like normal persons, excrete elevated levels of intermediates in the pyrimidine pathway when they are given Allopurinol. Presumably Allopurinol inhibits pyrimidine synthesis in them as well. Hence, an alternative theory of Allopurinol's action seems more attractive.

It is important to remember, however, that only *hemolyzates* from patients with the Lesch-Nyhan syndrome lack activity for the affected enzyme. Nucleated cells — at least fibroblasts cultured from patients with this disease — have significant levels of residual enzyme activity (Fujimoto and Seegmiller, 1970). Over a period of hours or days, these residual levels of activity might generate sufficient amounts of Allopurinol ribotide to inhibit pyrimidine synthesis. Such a mechanism would be particularly likely to apply if the amount of Allopurinol in the body, rather than the amount of enzyme, were the rate-limiting factor.

Patients who receive Allopurinol develop increased levels of the final two enzymes of pyrimidine synthesis (Fox and O'Sullivan, 1970). One of these enzymes is the one inhibited by the ribotides of Allopurinol and xanthine. Fox and O'Sullivan suggest that this increase may reduce the inhibition of pyrimidine synthesis and thus help the patient avoid the clinical consequences of pyrimidine starvation. Indeed, the rise in the cellular level of an enzyme, in response to an inhibitor of that enzyme, may

*See page 397.

conceivably be related to phenomena such as pharmacologic tolerance and the acquired resistance of tumor cells to antineoplastic agents (Krooth, 1968 and 1970).

In addition to Allopurinol and certain other agents Pinsky and Krooth, 1967), a rare autosomal recessive gene can inhibit pyrimidine synthesis in human cells. Persons who are homozygous for this gene are affected with Type I hereditary orotic aciduria; cells from such people have greatly reduced levels of the final two enzymes of pyrimidine synthesis. Fox and O'Sullivan argue that perhaps these last two enzymes of the pathway are part of an enzyme complex. I also favor this view; indeed I find it hard to formulate another theory as consistent with all the evidence accumulated on this disease over the past ten years. In addition, it has become clear that enzyme complexes, often of enormous molecular weight, are frequently encountered in living cells (Ginsburg and Stadtman, 1970)—especially (Fink, 1970) in those which, like the human cell, have a definite nuclear membrane ("eukaryotes").

These complexes are aggregates of enzymes. Each enzyme within the aggregate catalyzes a particular step in a metabolic sequence. For this reason, the aggregate itself catalyzes the whole of the sequence, or a good part of it. Such aggregates are thought to retain the intermediates in the sequence, so that each enzyme does not have to depend on accidental collision with its particular substrate to effect its step in the reaction chain. Only one collision is necessary—the aggregate and the substrate of the first enzyme. The pyruvate dehydrogenase complex recovered from mammalian tissue has several catalytic activities associated with it and a molecular weight of nearly ten million (Ginsburg and Stadtman, 1970). It seems like a good way to bring order into the confusion that would otherwise exist in the cytoplasm of a complicated cell.

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More than five million American women are overweight. These, of course, are round figures.

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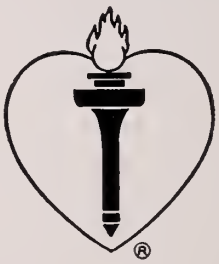
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Editor's Soliloquy

Our Australian Colleagues

WE ARE GRATEFUL to our worthy Australian colleagues for so generously allowing us to enter their Halls of Knowledge via their contributions to our journal, thus permitting us to profit from their valuable observation and experience.

We learn from each other. The high intellectual and moral principles and practices of doctors, coupled with their humanitarian propensity to disseminate their new discoveries and skills, categorize them as both students and educators. Perhaps more persistently and conscientiously than the members of any other profession the physician keeps himself abreast of progress, chiefly in the field of his own specialty. But, since no specialty is insular, its practitioner must be always alert to the importance and impact of his particular specialty within the total framework of medicine.

To that end he engages in voluminous and eclectic reading of scientific books, medical publications, and current research, all of which are global in scope and validity. By this Royal Road and no other could medicine have ascended to the height it now occupies, whence it can look back with genuine pride and ahead with eager anticipation.

Contrary to the policies and practices of many entrepreneurs in business, commerce, and industry, the physician never conceals his new find under a bushel, nor secretes it in a private vault, nor denies it to other doctors who might use it to advantage; rather he shares it gratuitously—with no other remuneration than the professional satisfaction of contributing to the alleviation and, hopefully, the elimination of human suffering.

Such diffusion of knowledge has been MINNESOTA MEDICINE's objective in sharing its pages with foreign colleagues, thereby achieving an international melding of medical theory and practice, speaking not just for one country but for the total world community.

It is in this spirit of free exchange that we salute our confreres in the Land Down Under and humbly thank them for sharing with us their priceless pearls of wisdom and insight.

Carl O. Rice, M.D.
Editor-in-Chief

Old Doc Hess says: Any mystery in a medical history distorts the facts and a reliable opinion, so that then there is no focus for sympathy or proper understanding.

Tit for Tat

A precocious five-year-old son of a professor asked his father what was the exact meaning of the verse beginning, "Humpty-Dumpty sat on a wall."

"In simple terms," said the professor, "it means Humpty-Dumpty perched on a vertical, solid structure; losing his equilibrium, he dropped from a higher to a lower level. Even the potentate's equestrians failed to succeed in assembling the fractured particles. Is that clear, son?"

"Absolutely," replied the son, "the lack of clarity in these alleged Mother Goose rhymes is amazingly apparent to one with an intellect above the moronic level."*

*M. Dale Baughman: Treasury of Stories.

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(Continued to Page 440)

Tumour Conference

Malignant Melanoma

The Diagnosis and Management

MALIGNANT MELANOMA is a tumour with a grizzly reputation and an incidence higher in Australia than in many other countries.[3,4] The author has treated over 700 patients suffering from maligant melanoma. Edward Barnes is a fictitious name given to one of my patients and his story shows many features that are typical of the diagnosis and the treatment sometimes used. His final progress is, unfortunately, most unusual but offers tantalizing opportunities for speculation and research.

Case History

Edward Barnes* was 59 when he first visited his physician in 1961 and reported that he had noticed a black spot on the left side of his back for about eight months. The spot had caused him little anxiety but he had noted that since it had first appeared, it had approximately doubled in size. Also, about one to two months before the visit he had noticed that the lesion itched slightly. The itch did not last for more than a day or two and was not bad enough for him to tear at the spot with his fingers, but he developed the habit of occasionally rubbing his back against a door or a piece of furniture. However, the irritation had a tendency to recur at intervals of two or three weeks, each time disappearing again as easily as it came. What finally convinced him to go to his physician was that he noticed, after showering and rubbing himself with a towel, that the black spot bled a little on to the towel. In addition, after work his wife noticed a small spot of blood about the size of a one-cent piece on his shirt.

Initial Examination

On examination, the patient had a lesion about 1 cm. in diameter at the level posterior end of the ninth rib. The lesion was almost uniformly black and only in one corner could a slightly paler area be detected. The surface of the black area, which was raised about 3 mm. above the skin, was glossy and intact, despite the history of previous bleeding.

On examination of the draining lymph nodes there was no evidence of enlargement or tenderness in the axilla, and no nodes were felt in the supra-clavicular region. In every other respect the patient appeared to be a healthy man of stated age. He was well built and his occupation (plumber) kept him in good physical condition.

He had been a resident in Australia from Europe for 20 years, during which he had been in good health. He had been vaccinated prior to immigration and had also been immunized against typhoid and tetanus. Apart from this he had never visited a physician.

The Primary Operation

His physician was not alarmed by the black spot and decided to leave it alone. By February 1963 (two years later), the lesion had enlarged further and his doctor removed it through a 2½ inch cut. The incision was closed and the wound healed without mishap. The pathology report was "malignant melanoma." The patient was told the nature of the lesion and no further treatment was advised at the time. However, he reported occasionally for check-ups.

Second Operation and Axillary Dissection

Nine months after the first operation in November 1963, Mr. Barnes noticed beneath the scar a small nodule which was neither uncomfortable nor discolored; however, as a precaution he thought it wise to visit the doctor. On this occasion he was referred to a surgeon and, within a week, he underwent a wide resection of the scar (subsequently shown to contain metastatic malignant melanoma). At the same operation he had an axillary node dissection, not in continuity with the side of the primary lesion. Both the surgeon and the patient were relieved to find that the nodes showed no histological evidence of malignancy. The only disturbing feature of the pathological examination was that a small cluster of malignant melanoma cells were found in a lymph vessel close to the primary site.

Extensive Dissection

A month after this operation, in December 1963, a small lump was found in the upper part of the axillary dissection. This was biopsied and found to contain metastatic malignant melanoma. It was at this stage that I first saw this patient and, although there was no other obvious evidence of malignancy, the position of his original scar indicated that the apex of the axillary had not been cleared at the original operation. Consequently it was decided that one of the few chances remaining for his survival might be to carry out a more thorough dissection of the axilla and also to explore supra-clavicular

*Fictitious name.

lymph nodes to ascertain if the disease had spread more proximally. A chest X-ray showed no evidence of metastatic disease in the lungs.

Accordingly, a supra-clavicular incision was made and revealed a black node at the junction of the sub-clavian and jugular veins. This node was removed and sent for frozen section examination. The report stated that its discoloration was due to carbon, presumably from the lungs, and did not contain evidence of tumour cells. As a result of this examination a full-scale excision of the supra-clavicular lymph nodes was carried out. This incision was then packed with a gauze and a second incision commenced below the clavicle and extended across the surface of the pectoralis major where it split into two parts to pass along the medial wall of the axilla to include the site of the primary lesion and a band of skin approximately four inches wide. The incision was deepened and the pectoralis major divided. The pectoralis minor was removed, together with a large mass of fat and fascia in the apex of the axilla and all subcutaneous tissues from the axillary dissection down to and including the site of the primary lesion. The large defect on the chest was then closed with a split skin graft and a drainage tube inserted into the axilla and the supra-clavicular incision closed.

Progress

Histological examination of the remainder of the supra-clavicular lymph nodes revealed evidence of metastatic melanoma in at least one lymph node; melanoma deposits were also found in the axillary lymphatics. The patient remained well for four months, when it was found that he had multiple (about 70) subcutaneous and intracutaneous nodules in the chest wall extending forwards from the site of the previous skin graft almost as far as the mid-line. However, he still had no evidence of generalized disseminated disease.

Chemotherapy

During the next two weeks, the patient was given a course of systemic chemotherapy (Treminon, Bayer), but without effect, because fresh nodules appeared and those already present, enlarged.

Vaccine Therapy

Accordingly, on 23rd April 1964, the patient was admitted to hospital, anaesthetised and, as far as possible, every visible or palpable tumour nodule was injected with a small quantity of attenuated smallpox vaccine (BP) (Commonwealth Serum Laboratories): a total dose of some 400 times the usual vaccination dose. Soon after the injection of virus the patient

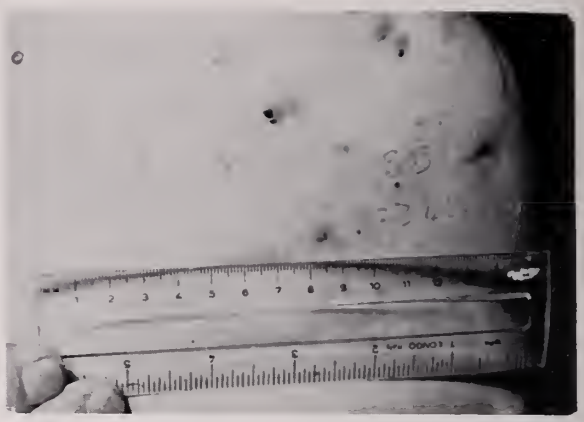


Fig. 1—Close-up of the chest wall of this patient taken on the 23rd April 1964. In the extreme right of the picture the lower edge of the skin graft may be seen. His nipple is above the area of this photograph.



Fig. 2—Larger view of the chest wall taken on 14th May 1964 as the vaccination reaction was subsiding. This gives some idea of the extent of the metastatic spread which reached nearly to mid-line.

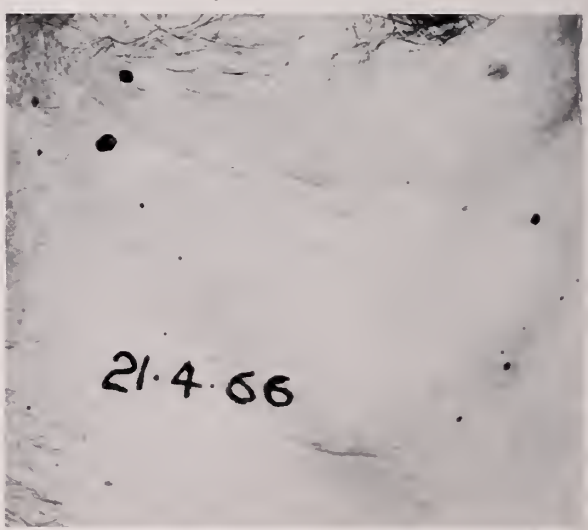


Fig. 3—Close-up of chest wall taken on the 21st April 1966. Note the complete disappearance of all metastatic deposits. The black spots in this picture are small haemangiomas. Careful scrutiny of the earlier photographs will reveal that they were present at that time. Patient's condition remains the same to this day.

showed a short rise in temperature for a few days, which subsided until the 5th day when he had rigor which gradually diminished in the next three or four days. The vaccination reaction over many sites was considerable but, as it subsided, the pigmented nodules became flat. In the following months the vaccinated nodules gradually became small blue-black stains. In the ensuing few years, the pigmentation at the site of the vaccinated nodules gradually disappeared and, at the time of writing in May 1970, the patient remains entirely well and free of all signs of disease. His chest wall at the site of the lesions is shown in Figures 1, 2 and 3.

Comments

Growth Rate

This patient describes several of the typical clinical features of malignant melanoma. He noticed the lesion had approximately doubled in size during a few months: the typical growth rate of a primary malignant melanoma. A lesion which enlarges at a constant rate over a period of many years is unlikely to be a malignant melanoma, but a spurt of growth in such a lesion may indicate malignant transformation. A lesion which grows over a period of days is more likely to be inflammatory than malignant. The typical growth is that described by this patient: an enlargement over a period observed during a few months.

The itch described by this patient is also typical of a melanoma and is present in about 25% of such cases.[11] The characteristic itch of a malignant melanoma is not severe; the patient usually rubs the lesion with his fingers rather than scratching or, as in this case, if the lesion is on the back, he may acquire the habit of rubbing it against a piece of furniture. The itch caused by a melanoma also tends to come and go spontaneously.

Bleeding

The bleeding described by this patient is also one of the typical features of malignant melanoma; it is usually caused by insignificant trauma (e.g., rubbing with a towel or friction with clothing) and consists of only a few spots of blood. The one cardinal clinical feature of malignant melanoma not mentioned by this patient is a progressive darkening of the lesion which the patient notices over a similar period to the enlargement, itch and bleeding.[6,7,8,9]

Although the clinical appearance of a malignant melanoma can take many forms, probably the most frequent appearance is smooth, glossy, black surface over at least part of the lesion.[6,7,8,9] If the lesion has been recently injured, the surface may be covered with a scab or crust. In the early stages the surface may be covered with fine keratin flakes.

Treatment

A lesson to be learned from this case is that if a patient presents with a black, enlarging, itching lesion which occasionally bleeds, it is vital to remove it immediately to establish a diagnosis. Even without the symptoms of itching or bleeding, a dark brown or black lesion which is *enlarging over a period of months* should be removed for biopsy.

Once the diagnosis of malignant melanoma is established it is important to institute thorough treatment and thorough follow-up. Although a form of follow-up was instituted, it was the patient himself who noticed the recurrence of the lesion as a small nodule in the scar nine months after the excision of the primary lesion. This is about the average time for local recurrence in the scar after inadequate excision of malignant melanoma.[5] This type of presentation is also typical of local recurrence in that the patient notices a painless nodule either close to, or directly beneath the scar of the original operation.

Although the site of this lesion made an incontinuity resection of the primary and lymph nodes a perfectly feasible operation, it was not done. I believe this to be a technical error in the management of this patient. The fact that the lymph nodes were negative on pathological examination is not necessarily of great significance, because a cluster of malignant melanoma cells less than 2 mm. in diameter can easily be missed in a routine sectioning of lymph nodes. Small clusters of cells are not detectable clinically and a negative histological examination, although a hopeful prognostic sign, does not exclude subsequent recurrence of the disease, as occurred in this case.

It is obvious that resection of tumours and lymph nodes, in this or any other malignant condition, is justified solely by the overall survival of patients. The pathological reports of

the removed tissue are of interest but do not establish the justification for operation. At present, there are no adequate comparisons available for the management of malignant melanoma between the extensive radical resections and smaller local removal of the disease.

Prognosis

The penetration of malignant melanocytes into a lymph vessel close to the primary site is certainly an ill omen. Metastatic melanoma occurs as frequently in lymphatics as in lymph nodes.[5]

A frequently carried out form of axillary dissection for malignant melanoma is to perform the operation through an incision which runs along the anterior axillary border and a short distance down the upper arm. This gives a good cosmetic scar, but the approach to the apex of the axilla is inadequate. This is the procedure which was carried out in the present case and shows a feature seen after such an operation, namely, recurrence in the apical axillary lymph nodes which were not removed at the time of the original operation. The clinical detection of the involvement of the apical axillary nodes is easy when the pectoralis major muscle is pushed forward immediately below the clavicle. However, this is a late sign and means there is considerable enlargement of the apical nodes.

Black lymph nodes at the junction of the subclavian and jugular veins is not an uncommon finding, the blackness due to carbon pigment, presumably from the lungs. If the future of the patient is to be determined by the appearance of the nodes it is important that the node at this site should be submitted to frozen section examination. Deeply discoloured lymph nodes may occur at other sites, but when this happens the pigment is melanin which has been absorbed into the lymphatics from nearby melanoma deposits. The nodes at the root of the neck are the only ones likely to be found to contain carbon as an explanation for their black appearance.

Rapid recurrence of tumour close to the scar is a common feature of spreading melanoma. The pattern of this type of recurrence is as described here: a series of cutaneous or subcutaneous nodules appearing to spread out very rapidly from the site of the previous operation. A carcinoma of the breast or any other malignancy which involves the skin and subcutaneous tissues does so by infiltration; not so the melanoma which produces a series of isolated lumps.

Virus Treatment

The use of viruses in the management of malignant disease has been a tempting possibility for many years. The first application of it was probably in 1912,[2] and since then there have been sporadic efforts to produce or use a virus which would be valuable in the treatment of malignant disease. On the whole, the results of this method of treatment have been very discouraging and the use of viruses in the treatment of carcinoma has been largely abandoned. Burdick[1] described a patient with malignant melanoma who was treated by attenuated smallpox vaccine and showed considerable improvement. It was pointed out in the discussion of his paper that the tumour regression in his patient could have been due to a spontaneous regression unrelated to the use of vaccinia. On being informed of these experiments by Dr. J. C. Belesario of Sydney, I commenced the use of vaccinia virus innoculation in a large number of patients suffering from advanced malignant melanoma to ascertain if tumour regression following the use of vaccinia was more frequent than spontaneous regression. To date, there have been more than 60 patients treated with attenuated smallpox vaccine on multiple melanoma sites, and the results of the early part of this work have been published.[10]

Patients who have systemic disease in the shape of cerebral, pulmonary, or hepatic metastases are unlikely to show any regression of the disease following the use of vaccinia. However, in patients of the type described here, where there are multiple cutaneous nodules which can easily be penetrated by injecting the vaccine directly into the substance of the nodules, there is a better than 10% chance of obtaining considerable regression. This is too frequent to be explained solely on the basis of spontaneous regression. It follows that although the use of attenuated smallpox is of very little value in the patients with systemic malignant melanoma, there are those in whom spread in the early stages is confined to the scar or its immediate vicinity, and the use

of vaccinia may produce a profound effect on the progress of the disease as described in this case. This patient is not unique in the series as there are five other patients who have survived for prolonged periods following vaccinia therapy.

G. W. Milton, F.R.C.S., F.R.A.C.S.*

*Professor of Surgery, Department of Surgery, University of Sydney, Sydney, N.S.W.

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Your Ulcer-Indigestion Index

If you have ever had an ulcer in your stomach or duodenum, you have a proved tendency toward this condition and should take every available step to keep the situation under control. Repeated episodes of nervous indigestion and heartburn also indicate a severe tendency toward emotion-generated digestive upset. But even if you never have suffered these miseries, you may have a mild tendency toward ulcer and indigestion which you can readily combat before it leads to trouble. Add up these scores:

20 points if you're a man. Duodenal ulcers strike eight times as often among males, with stomach ulcers equally common in both sexes.

20 points if you have a long, narrow chest and stringbean build. You're less prone to gall bladder disease with this type of body, but much more prone to ulcer.

20 points if your duties involve taking a lot of guff either from customers, superiors, or companions forced upon you by your position.

20 points if you personally make most of the big decisions regarding your own family's welfare.

20 points if you haven't turned to any other member of your family for advice on an important matter in the last three months.

A total score of 60 or more gives you a more-than-average chance of having digestive troubles. Eighty or 100 makes definite steps to cut this risk worthwhile.*

*John E. Eichenlaub: The Minnesota Doctor's Home Treasury of Unusual Stress Easers, 1964.

Classified Advertisements

(Continued from Page 434)

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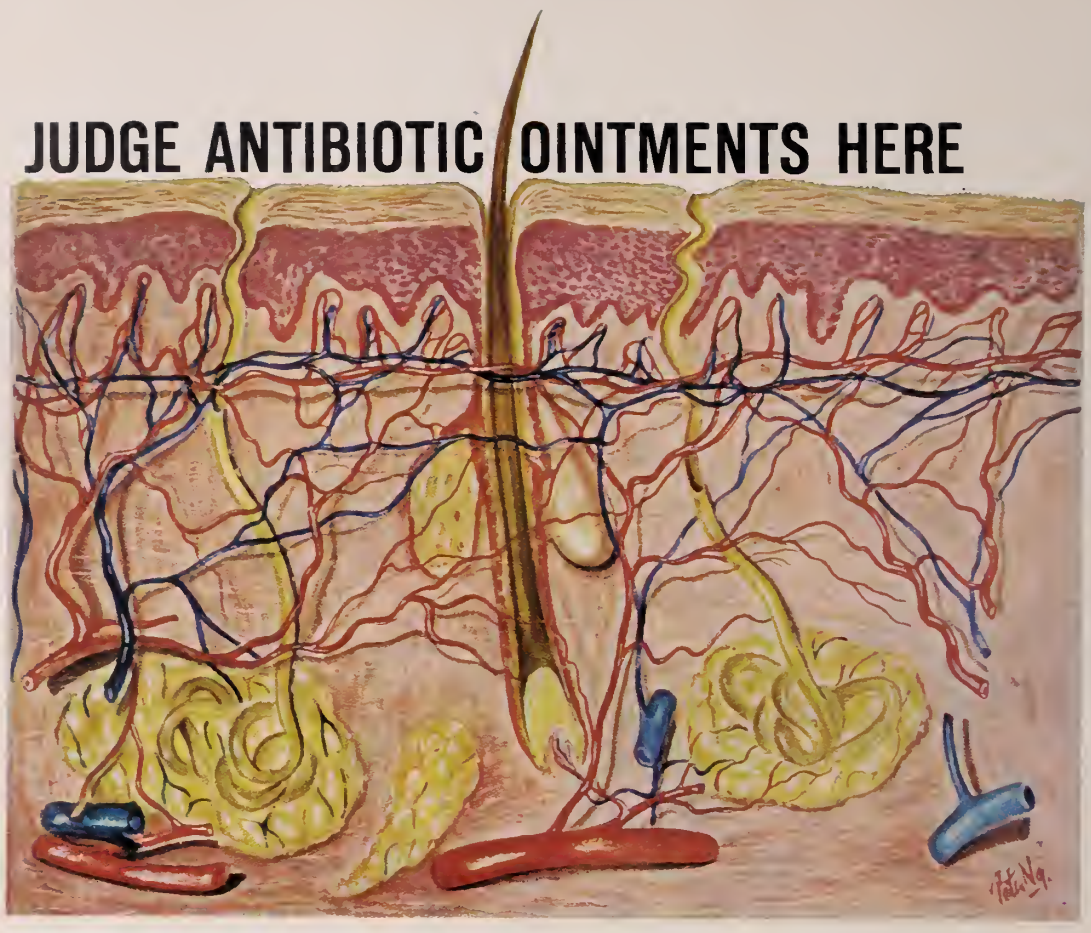
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Fracture Conference

Supracondylar Fractures of the Humerus in Children

SUPRACONDYLAR FRACTURES are the commonest injury about the elbow joint in children. They are of special significance because of the unique response of this joint to injury, be it intractable stiffness following minor trauma, its remarkable sensitivity to early passive movement, the rare incidence of myositis, or the even rarer complication of ischemic contracture.

These fractures occur most frequently in the three- to nine-year age group and are quite rare in infancy. The sex incidence is approximately equal.

The purpose of this paper is to review the mechanism of injury in supracondylar fractures with particular reference to treatment and the management of complications.

Mechanism of Injury

Posterior displacement—Extension type

This is most frequently caused by a fall onto the oustretched hand with

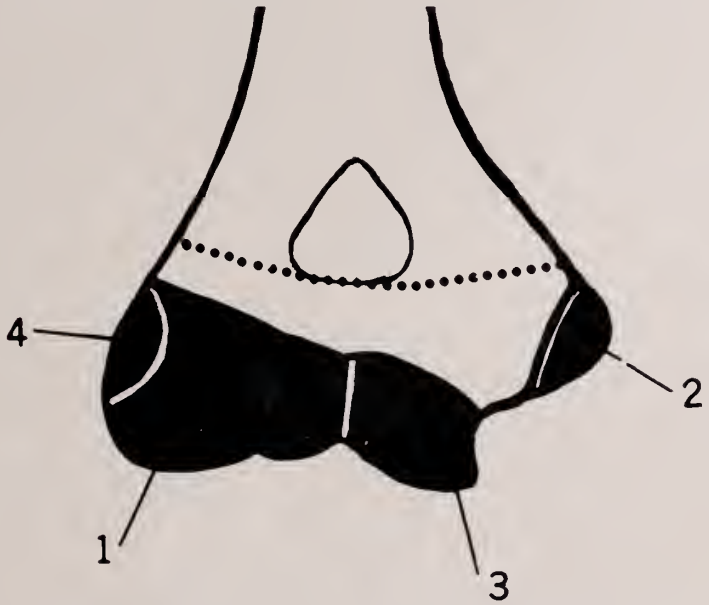


Fig. 1—Diagram illustrating the secondary ossification centres (epiphyses) at the distal end of the humerus—1. capitellum, 2. medial epicondyle, 3. trochlea, 4. lateral epicondyle. These centres appear at approximately 3, 6, 9 and 12 years respectively.

the elbow bent. The fracture pattern and the coronal and rotary displacement depend upon the position of the arm at the time of impact. A fall forward with the hand outside the line of the body pronates the distal fragment, while a fall backwards with the hand inside the body line supinates it.

Anterior displacement—Flexion type

A fall or blow on the point of the elbow or a fall backwards onto the fully extended arm may produce this fracture. It is a rare injury (2% of all cases) and will not be discussed further.

Supracondylar fractures differ from the common metaphyseal fractures in that they do not occur through a growth plate but at the weakest part of the distal humeral shaft near the olecranon and coronoid fossae well proximal to the secondary ossification centres (Figure 1).

Soft tissue stability is provided on the lateral side of the fracture by the brachioradialis and extensor carpAradialis longus, posteriorly by the triceps and anteriorly by the brachialis; there is none on the medial side, but here bony stability is usually available.

Neurovascular Structures at Risk

Artery

The brachial artery, to some extent cushioned by the brachialis muscle, may be stretched across the sharp anterior edge of the proximal fragment if displacement is severe, and is rarely directly injured by it. More often, contusion or stretching is held responsible for ischemic complications. These may be aggravated and even initiated by excessive flexion of the swollen elbow after reduction, or by encircling bandages and plaster casts. Changes in the collateral circulation may also be implicated.

Nerves

The three major nerves in the region of the elbow joint may all be damaged. If injured, the *median nerve* is usually contused, resulting in neuropraxia or axonotemesis, while the *radial* and *ulnar nerves* most often suffer mild traction lesions. Many authors report the *radial nerve* as that most frequently involved, but in our experience it is the *median*. The posterior fibres of the median nerve are at particular risk, and damage to them results in weakness or paralysis of the flexor digitorum profundus to the index finger.

Management

First Aid

The most effective and comfortable way to transport a child with a supracondylar fracture is to support the arm in a simple triangular sling.

Examination and Assessment

Careful examination of sensation, motor power and circulation in the hand is mandatory. Rapidly increasing swelling is an indication for urgent reduction and may herald vascular complications. X-ray examination of the elbow in two planes is essential despite convincing physical signs. This will show the direction and degree of displacement far better than clinical assessment which may be hampered by swelling. As in all elbow injuries in children, comparative x-ray views of the normal elbow may be of great assistance.

Anaesthesia

These fractures must be reduced as soon as possible. General anaesthesia is desirable and superior. If contraindicated, brachial plexus block may be employed providing it will not confuse the evaluation of nerve damage.

Examination of the Fracture

The first phase of fracture reduction is, in fact, the final stage of physical examination. The distal fragment is palpated to assess its directional instability and rotary displacement. Rotation can be measured by comparing the angle made by a line through the epicondyles with the horizontal on the injured and normal sides, with the humerus fixed in full external rotation and the elbow flexed to 90 degrees (Figure 2).



Fig. 2—Photograph demonstrating the method used to estimate rotation of the distal fragment. The angle formed between a line joining the epicondyles and the horizontal is estimated when the humerus is fully externally rotated at the shoulder joint and the elbow flexed to approximately 90 degrees. Note how the point of the elbow is ahead of the posterior surface of the arm.

Reduction

Nearly all fresh fractures can be anatomically reduced if swelling is not severe.

As with all fractures, the distal fragment, here best considered as the lower humeral fragment and forearm bones together, should be manipulted in the opposite direction to the casual force.

(a) *Traction.* Firm traction with counteraction (a rolled towel in the axilla is effective) is applied until the coronal displacement is corrected and sufficient distraction has been obtained to allow manipulation. Traction may be effected either (1) with the elbow flexed 60 degrees which many feel avoids stretching the vessels and nerves or (2) with the elbow fully extended which aids in correcting the carrying angle.

(b) *Manipulation.* The distal fragment is grasped between the thumb and forefinger of the examiner's hand, adjusting the tilt and rotary displacement. The contiguous jagged edges are then locked together by forward pressure on the distal fragment with the thumb. Occasionally, hyperextension of the elbow may be required to "hook" the fragments together.

(c) *Flexion.* At this stage the elbow is flexed and, in so doing, the fingers are moved over the anterior surface of the lower humerus as a counter force against thumb pressure (Figure 3). The more flexion obtained, the greater the stability. Reduction is unstable if the elbow cannot be flexed above a right angle (Figures 4 A and B). The degree of elbow flexion permissible depends on the amount of swelling present and, ultimately, on the circulation in the hand and fingers.

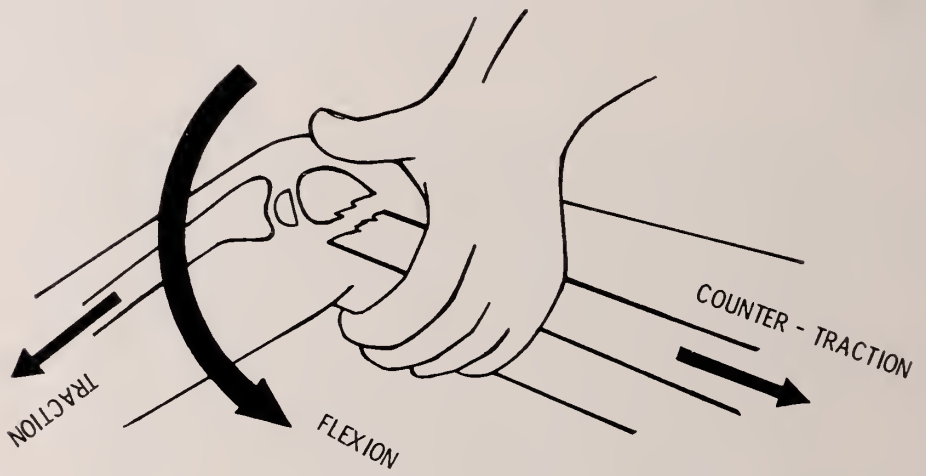


Fig. 3—Diagrammatic representation of the crucial phase in reduction of an extension type supracondylar fracture. The elbow is flexed, still maintaining traction and countertraction. The thumb pressure on the distal fragment is countered by the backward force exerted from the surgeon's fingers.



Fig. 4—(A) Lateral radiograph of the elbow of a child aged 5 years in whom a supracondylar fracture has been significantly overreduced. The joint is held by a plaster slab at a right angle. (B) A lateral radiograph made ten days after the film shown in A. The position has further deteriorated and there is obviously gross rotational malalignment, the view of the distal humerus being that normally seen in an antero-posterior projection. Position has been lost because the fracture was inadequately reduced initially and insufficient flexion was gained to maintain reduction.

Clinical Assessment of Reduction

If the fracture is reduced, the point of the elbow should lie slightly in front of the posterior surface of the arm (Figure 2).

Rotation is checked as already described (Figure 2).

Maintenance of Reduction

A simple collar and cuff is all that is required to hold the elbow flexed and so maintain stability (Figure 5).

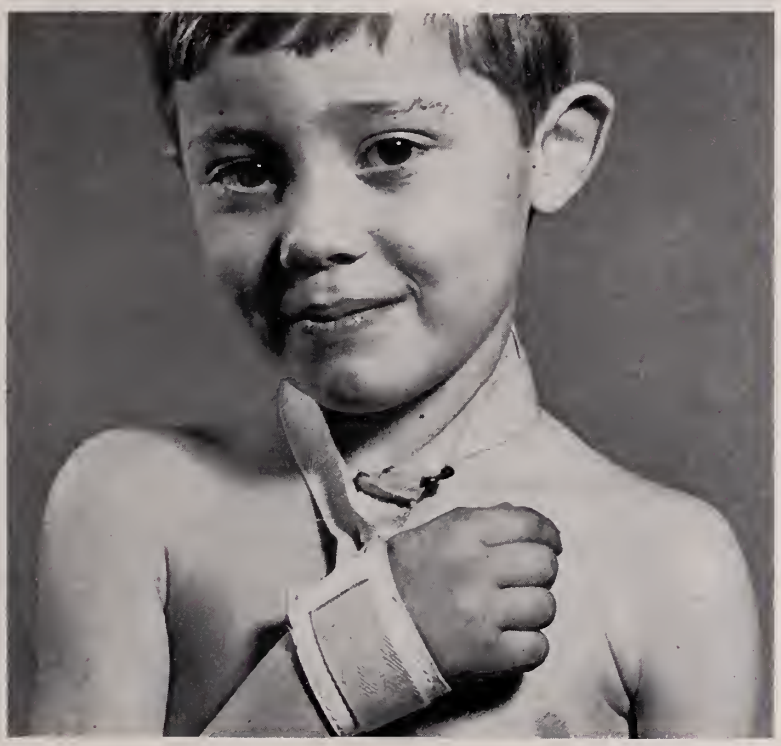


Fig. 5—Photograph of a child wearing a collar and cuff.

Post-Reduction X-Rays

With the child still anaesthetised, antero-posterior and lateral radiographs are made without removing the collar and cuff. In order to demonstrate the distal humerus in the A-P film, the x-ray beam must be tilted 15 degrees from the vertical. Both medial and lateral cortices must be anatomically reduced for correction of lateral shift and rotation. Moderate antero-posterior displacement is acceptable, as this is the only deformity which will correct with remodelling.

Problem Cases

Unstable Fractures

Occasionally, a plaster slab is necessary to control pronation or supination in order to lock the fragments together. Any form of encircling plaster is contraindicated.

Infrequently, reduction cannot be held because of extensive disruption of soft tissues or of fracture of the anterior beak (Figures 6 A and B). Here, a safe alternative method of treatment is modified Dunlop traction (Figure 7). Overhead skeletal traction is not considered either safe or truly effective in controlling rotation of the distal fragment.

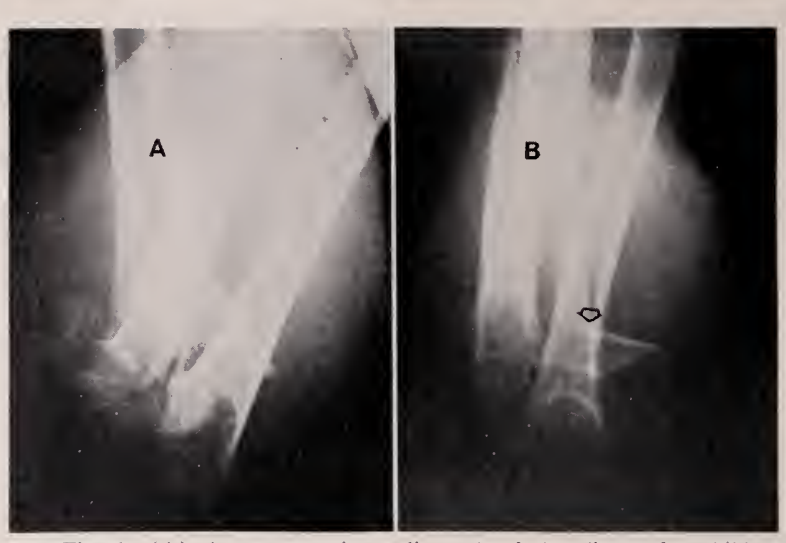


Fig. 6—(A) Antero-posterior radiograph of the elbow of a child aged 5 years who sustained a displaced supracondylar fracture. The medial beak is well shown in this pre-reduction film. (B) Antero-posterior view obtained after the first attempt at manipulation. The medial beak has been fractured (arrow) and this has resulted in marked instability at the fracture site.



Fig. 7—Photograph demonstrating modified Dunlop traction for the treatment of unstable, posterior supracondylar fractures. Note the arrangement of the slings which are taped to the skin. Two or three pounds of traction at each point are usually sufficient.

The Late Case

The case received *several days after injury*, provided swelling is not marked and there are no neurovascular complications, should be treated as a fresh injury. In the event of gross swelling, preliminary Dunlop traction with elevation is often effective in maintaining a satisfactory position until swelling subsides, when manipulative reduction can be performed.

The case received *more than two weeks after injury*, by which time union is well advanced, is best managed by leaving the fracture site undisturbed and correcting deformity by osteotomy after full joint motion has been regained.

Surgery

Open reduction plays no part in the management of uncomplicated fractures. The procedure described above precludes the necessity for surgical intervention which almost invariably leads to some loss of joint motion.

Post-Reduction Management

Repeated neurovascular assessment in the first 24 hours is essential. Increasing pain, unrelieved by analgesics and aggravated by active or passive extension of the fingers, is an omen of impending muscle ischemia.

Repeated clinical assessment should alert the surgeon to loss of fracture position. Stability is maintained by increasing flexion as the swelling subsides.

All children with displaced supracondylar fractures of the humerus should remain in hospital in the care of trained observers until the swelling has subsided sufficiently to allow elbow flexion to 120 degrees.

Repeat radiographs at one week. Remanipulation should be undertaken if position is lost in the first seven to nine days, but it must be gentle. Repeated manipulations to maintain anatomical alignment are potentially harmful.

The collar and cuff is retained inside the clothing for two weeks. In the third week, the child may put his arm through the sleeves and wear the collar and cuff outside while the degree of flexion is gradually reduced to 90 degrees. At the end of three or four weeks the sling may be removed and active exercises begun. Unstable fractures are held for four weeks and the plaster slab is used in the first two.

Active movements are encouraged. Passive exercises, particularly by a physiotherapist, are strongly contraindicated.

Early Complications

Arterial Injury

The brachial artery cannot be trapped or angulated if anatomical reduction is achieved. *If the radial pulse is absent on initial examination* the urgency for prompt reduction must be emphasized. However, the pulse usually returns when the fracture is reduced. *If the radial pulse is absent following reduction,* provided peripheral circulation and capillary return are adequate, there is time for observation and reassessment, but a blue or white hand with cold or numb fingers prompts the following steps: remove any encircling bandages, reduce the degree of elbow flexion, if necessary convert to Dunlop traction, re-x-ray, and if indicated, re-reduce the fracture. If no response, operate.

Insufficient information is available to clearly indicate the correct course to follow if operation is needed, but many surgeons recommend exploration of the brachial artery and either ligation or excision of the spastic segment of the artery if it fails to improve after bathing in warm saline or papaverine. If transected, the artery can be ligated, but the place of arterial reconstruction is presently undefined. Others, including the present authors, are of the opinion that the artery should not be explored initially but that wide fasciotomy should be performed to relieve tension within the flexor compartment of the forearm. After 10 hours of ischemia, there is no reason to expect that any benefit can accrue from arterial surgery because of irreversible muscle damage.

Nerve Injury

Neuropraxia, which recovers within six weeks, is the commonest injury to all nerves. An expectant course is adopted. Exploration is deferred until clinical and electromyographic evidence of failed regeneration is obtained.

Late Complications

Vascular

Volkmann's ischemic contracture causes a disabling deformity of the hand which may be improved by reconstructive surgery. Function may be compromised further by ischemic neuritis and more extensive involvement of all forearm muscle groups.

Malunion

Most writers have shown conclusively that alteration in the carrying angle is by far the commonest complication of these fractures. Cubitus varus, due either to pronation or to medial tilt of the distal fragment, is the commonest late deformity and produces an unsightly appearance but with little loss of function (Figure 14). Cubitus valgus is less common and less deforming but carries with it the risk of delayed ulnar neuropathy. Both these deformities, which result from tilt or rotation of the distal fragment, are amenable to corrective osteotomy. Disturbance of the growth centres plays little or no part in their production.

Myositis Ossificans

This unusual complication is an enigma. It results primarily from periosteal and soft tissue injury in the region of the fracture. It requires no treatment but passive exercise is harmful. If a bony mass persists as a block to movement it can be excised.

Case Reports

Case 1.

A female child, aged six years, fell forward onto the outstretched right hand with the elbow flexed, sustaining a supracondylar fracture of the humerus (Figure 8). The patient reported to the hospital within ten minutes of injury. On examination the right radial pulse was distinctly weaker than the left but the peripheral circulation was quite adequate; she was unable to flex the right index finger. Initial sensory examination of the hand did not reveal anything remarkable, but when reexamined immediately before manipulation two hours after the injury, some sensory loss was noted in the index finger and thumb. The fracture was manipulated under general anaesthesia and an excellent reduction obtained (Figures 9 and 10). The radial pulse returned immediately. Collar and cuff immobilization was used and the patient remained



Fig. 8—Case 1. Antero-posterior (A) and lateral (B) radiographs showing a markedly displaced posterior extension type supracondylar fracture. Note the degree of comminution laterally and the prominent antero-medial spike. The epiphyses for the capitellum and the medial epicondyle are present.

in the hospital for three days until the swelling had subsided sufficiently to allow elbow flexion to 120 degrees. Progress radiographs at one week showed no change in the position of the fracture.

The collar and cuff were retained inside the clothing for two weeks and then worn outside for a further week, when it was discarded. At two months post injury the only abnormality of movement was a 15-degree loss of extension. The median nerve injury had recovered apart from a slight residual sensory impairment. Full interphalangeal joint flexion of the index finger was regained within six weeks. At three months after injury, a full range of elbow movement was present and the carrying angle normal, with no detectable sensory loss in the hand.



Fig. 9—Case 1. Antero-posterior (A) and lateral (B) radiographs made after the first attempt at manipulation. In the lateral view the position is almost acceptable but the slight gap anteriorly suggests incomplete reduction. The antero-posterior view demonstrates a significant gap medially and some tilting of the distal fragment.



Fig. 10—Case 1. After re-manipulation, the antero-posterior (A) and lateral (B) radiographs show improvement in the position of the fracture. In the lateral the reduction is anatomic and in the antero-posterior projection the medial cortex is also anatomically aligned. The degree of comminution laterally is now clearly demonstrable. Note the degree of flexion obtained, which enhanced stability of the reduction.

Comment

This patient clearly illustrates the natural history of a neuropraxia and, in addition, the appropriate management when the radial pulse is impaired: prompt anatomic reduction.

Case 2.

A seven-year-old female child fell from a horse and sustained a supracondylar fracture (Figure 11). The arm was supported in two wooden splints when she arrived at the hospital two hours after the injury. On examination the elbow was grossly swollen and deformed. The radial pulse was present and the capillary circulation normal. There was a slight impairment of sensation in the median nerve distribution in the hand.



Fig. 11—Case 2. Antero-posterior (A) and lateral (B) radiographs of the elbow showing a markedly displaced supracondylar fracture of the extension type. In this fracture the distal fragment is medially displaced (Figure 8). Note the prominent medial beak and the obvious rotary malalignment in the lateral projection.

The fracture was reduced under general anaesthesia five and a half hours after the injury, two manipulations being required (Figures 12 and 13). The final position was considered satisfactory but, as the fracture was quite unstable, a plaster slab was used to hold the forearm in supination because of a tendency for the medial side of the fracture line to open up in pronation. The patient remained in the hospital for four days until the swelling had subsided and the elbow could be adequately flexed. Repeat radiographs on the day of discharge showed that the position had been maintained.

The plaster slab was removed on the sixteenth day post injury, but the collar and cuff were retained inside the clothing until the twentieth day. After this time it was worn outside the

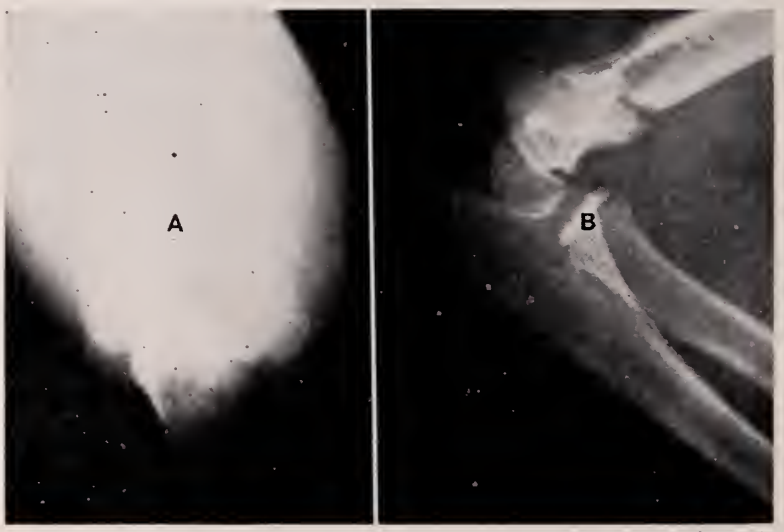


Fig. 12—Case 2. Antero-posterior (A) and lateral (B) radiographs made after the first attempt at reduction. In the lateral view the anterior humeral cortices are overlapping but the general alignment appears satisfactory. The antero-posterior radiograph, however, shows medial displacement of the distal fragment and significant lateral tilt.

clothes until four weeks post fracture. Elbow motion was rapidly regained, and two months after injury the patient lacked only 10 degrees of extension. At three months the range of motion was normal and the carrying angle the same as that on the opposite side.

Comment

Obviously it would have been a distinct advantage to have reduced the fracture much earlier. Nevertheless, the subsequent course illustrates the routine management of an unstable supracondylar fracture. The rate at which function was regained can be considered average for this fracture.



Fig. 13—Case 2. Antero-posterior (A) and lateral (B) radiographs made after a further manipulation. Anatomic reduction has been obtained and the degree of flexion of the elbow joint ensures stability.

Case 3.

A seven-year-old girl fell onto an outstretched hand and sustained a severely displaced posterior extension type supracondylar fracture. Closed reduction was attempted within four hours of injury, but this could not be achieved because of comminution and swelling. The child was returned to the ward with instruction to keep the arm and the hand elevated. At thirteen hours after injury, the hand was found to be white and insensitive. The radial pulse was absent. One hour later the antecubital fossa was explored. The brachial artery was isolated proximally but it could not be traced distally because of gross oedema, haematoma and distortion of the anatomy; the vessel was in marked spasm. An extensive fasciotomy of the forearm was performed and then the radial pulse returned, together with adequate capillary circulation in the hand. The arm was subsequently managed in modified Dunlop traction with elevation and the patient did not develop ischemic muscle contracture. The position of the fracture was disregarded.

One year after injury a full range of elbow motion had been regained but with a significant residual gun-stock deformity due to cubitus varus (Figure 14). At two years after the injury



Fig. 14—Case 3. Photograph demonstrating the unsightly gun-stock deformity.

a corrective osteotomy was carried out with excision of a lateral wedge and correction of rotation (Figure 15). Full movement of the elbow joint was rapidly regained and was normal six months after operation. Since that time the patient has led a normal life and takes part in all sporting activities.

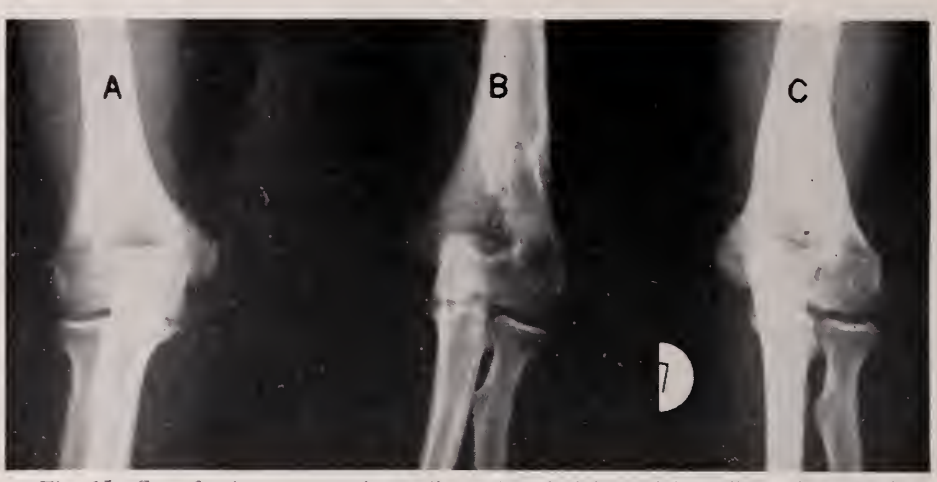


Fig. 15—Case 3. Antero-posterior radiographs of right and left elbows in extension (A) and (B) demonstrating marked cubitus varus on the left. The correction obtained by osteotomy is demonstrated in the antero-posterior projection (C) made four years after operation.

Comment

The operative findings in the antecubital fossa are typical of what is usually found at exploration. Fasciotomy probably averted significant ischemic contracture, but in this instance the exact time period of forearm muscle ischemia is not known. The case clearly demonstrates the value of continued clinical observation.

Summary

Supracondylar fractures in young children are best managed conservatively. Provided manipulation is carried out promptly under full anaesthesia and with x-ray control, an experienced surgeon with a clear appreciation of the mechanisms of injury should be able to reduce almost all supracondylar fractures without recourse to preliminary traction or operative intervention.

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An obstinate man does not hold opinions. They hold him.—Marshalltown Times-Republican

Case Report

Spinal Muscular Atrophy

J. G. McLEOD, M.B., D.Phil., M.R.A.C.P.* and I. M. WILLIAMS, M.B., B.S.†

SPINAL MUSCULAR atrophies are a group of diseases which are characterized by progressive anterior horn cell degeneration. Two major types, Werdnig-Hoffman disease (infantile spinal muscular atrophy) and Kugelberg-Welander syndrome (juvenile spinal muscular atrophy) are usually distinguished on the basis of the age of onset and the rate of progression of the disease. Werdnig-Hoffman disease begins, characteristically, during the first year of life, with muscular weakness which runs a rapidly progressive course.[1,2] By contrast, in the Kugelberg-Welander syndrome symptoms of proximal muscular weakness usually commence in infancy or childhood and progress very slowly over a period of many years.[3]

In this paper, twelve cases of spinal muscular atrophy of both Werdnig-Hoffman and Kugelberg-Welander types are described, and the relationship between the two disorders is discussed.

Case Material

Twelve patients with spinal muscular atrophy have been examined. The diagnosis was established by means of electromyography and muscle biopsy.

Electromyography

Selected muscles were sampled with concentric needle electrodes. The muscle action potentials were amplified, displayed on an oscilloscope, and photographed on 35 mm. film. In all the patients examined in the present series there was definite evidence of chronic partial denervation, characterized by a reduction in the interference pattern on maximum voluntary effort with polyphasic units of large amplitude and long duration firing in relative isolation (Figure 1). Motor conduction velocities were determined in the median, ulnar or lateral popliteal nerves and were within the normal range, or only slightly reduced.

Muscle Biopsy

Muscle biopsy was performed in 11 of the 12 patients, and in the case of one patient autopsy material was also available. In 10 patients there was definite evidence of neurogenic atrophy characterized by groups of atrophic fibres in otherwise normal fasciculi (Figure 2). In the other case, only fat and fibrous tissue were seen in the biopsy specimen.

The cases were divided into two groups according to the age at onset of symptoms. Group I consisted of six patients in whom muscle weakness and wasting became apparent during the first year of life and may be classified as infantile spinal muscular atrophy, or Werdnig-Hoffman disease. Group II consisted of the remaining six patients in whom muscle weakness and wasting developed after the first year of life and may be classified as juvenile or adult spinal muscular atrophy of the Kugelberg-Welander type.

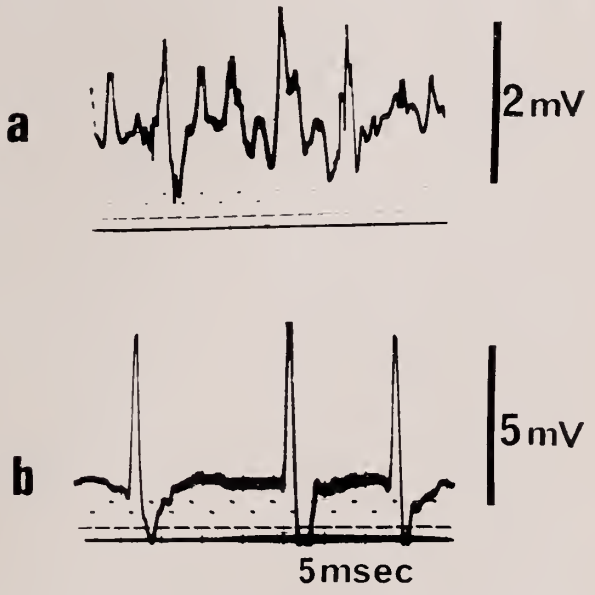


Fig. 1—Electromyographic recordings from (a) control subject, (b) patient with Kugelberg-Welander syndrome (Case 11), in which large amplitude units firing in relative isolation are conspicuous.

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See editorial, page 429.



Fig. 2—Transverse section of gastrocnemius muscle from patient with Werdnig-Hoffman disease (Case 2). There is marked variability in fibre size; some fibres of normal diameter lie next to markedly atrophic fibres.

Infantile Spinal Muscular Atrophy (Werdnig-Hoffman Disease)

All six patients developed clinical features of muscle disease within the first year of life, and four of them were observed to be hypotonic at birth (Table 1). Weakness and wasting were more pronounced and reflexes were absent in the lower limbs of all the patients. Muscle fasciculation was not a prominent feature in any of the cases.

The disease ran a rapidly progressive course in five patients, but in Case 1, where there was a later onset of the disease, the child was alive at the age of two and a half years although unable to support his weight with the lower limbs. There was no family history of the disease nor any history of parental consanguinity in any of the patients.

Juvenile and Adult Forms of Progressive Spinal Muscular Atrophy (Kugelberg-Welander Syndrome)

In four of the six patients, the onset of muscular weakness occurred in the first decade, but in the other two the symptoms did not develop until adult life (Table 2). In all cases the

TABLE 1.

Clinical Features and Results of Investigations of Patients with Spinal Muscular Atrophy

Group 1—Werdnig-Hoffman disease.

Case	Sex Age	Age of Onset	Family History	Physical Signs	E.M.G.	Motor Conduction	Muscle Biopsy
1.	M 2½ years	12 months	—	Weakness, wasting, absent reflexes of lower limbs.	Denervation	Lateral popliteal nerve, 42M/Sec.	Neurogenic atrophy
2.	F 1 year	6 months	—	Weakness, wasting, absent reflexes of upper and lower limbs.	Denervation	Ulnar nerve, 56 M/Sec.	Neurogenic atrophy
3.	F 3 months	birth	—	Hypotonia, absent reflexes, weakness and wasting of lower limbs.	Denervation	—	Neurogenic atrophy
4.	F 9 months	birth	—	Hypotonia, generalized wasting and weakness, absent reflexes.	Denervation	Median nerve, 30 M/Sec.	Neurogenic atrophy
5.	F 6 months	birth	—	Hypotonia, absent reflexes.	Denervation	—	Fat and fibrous tissue only
6.	F 7 months	birth	—	Hypotonia, absent reflexes.	Denervation	—	Neurogenic atrophy

weakness and wasting showed predominantly a limb-girdle distribution, although in long-standing cases the trunk and distal muscles were also affected (Figures 3, 4). In all patients except Case 8, the weakness was more pronounced in the lower limbs. In none of the patients, was there any clinical involvement of facial or bulbar musculature or of the pyramidal tracts, and muscle fasciculation was not observed. Except for Case 9, who had an affected sibling, there was no family history of the disease, and parental consanguinity was not reported by any of the subjects.

In four patients the disease has run a slowly progressive course for periods ranging from 15 to 50 years. By contrast, one child (Case 7) is so severely disabled that at the age of five she is unable to stand or sit.



Fig. 3—Case 10. Note atrophy of shoulder girdle musculature and lumbar lordosis.

Discussion

There was definite electromyographic evi-

TABLE 2.

Clinical Features and Results of Investigations of Patients with Spinal Muscular Atrophy
Group 2—Kugelberg-Welander syndrome.

Case	Sex Age	Age of Onset	Family History	Physical Signs	E.M.G.	Motor Conduction	Muscle Biopsy
7.	F 9 years	1-2 years	—	Proximal muscle weakness of limbs, especially lower. Reflexes present. Plantar responses flexor.	Denervation	Lateral popliteal nerve, 50 M/Sec.	Neurogenic atrophy
8.	M 53 years	35-40 years	—	Limb girdle weakness, especially of upper limbs. Reflexes present. Plantar responses flexor.	Denervation	Lateral popliteal nerve, 43 M/Sec.	Neurogenic atrophy
9.	F 56 years	2 years	1 Sister affected	Limb girdle weakness, more pronounced lower limbs. Absent reflexes. Plantar responses flexor.	Denervation	Median nerve, 64M/Sec.	—
10.	F 49 years	20-25 years	—	Lumbar lordosis. Limb girdle muscle wasting and weakness, especially lower limbs. Reflexes depressed. Plantar responses flexor.	Denervation	Lateral popliteal nerve, 51 M/Sec.	Neurogenic atrophy
11.	M 5 years	1-2 years	—	Generalized muscle weakness and wasting, more pronounced lower limbs. No facial weakness. Absent reflexes. Plantar responses flexor.	Denervation	Lateral popliteal nerve, 48 M/Sec.	Neurogenic atrophy
12.	M 51 years	2 years	—	Generalized muscle wasting and weakness, more pronounced in lower limbs and proximal muscles. Reflexes absent. Plantar responses flexor.	Denervation	Median nerve, 50 M/Sec.	Neurogenic atrophy

dence of chronic partial denervation in the muscles of all the patients, and motor conduction velocities in the peripheral nerves were normal or only slightly reduced. These electrophysiological findings indicate the presence of widespread disease of anterior horn cells, or possibly motor roots, and were supported by the pathological evidence of neurogenic atrophy in the muscle biopsies.

The patients in Group 1 have the clinical features of Werdnig-Hoffman disease, including onset of muscle weakness predominantly in the lower limbs during the first year of life with rapid progression.[4]

Although the uniformly fatal nature of the disease is often stressed,[1] a number of authors have drawn attention to the fact that prolonged survival may occur.[4,5] Byers and Banker[2] suggested that the disease ran a more benign course in those infants in which the onset occurred later.

Kugelberg and Welander[3] described a more benign, slowly progressive form of spinal muscular atrophy with an onset in the first two decades in which proximal muscle weakness



Fig. 4—Case 12. There is generalized muscle wasting, including the distal muscles of the lower limbs.

was the main symptom. The patients comprising Group 2 of the present report have the characteristic clinical, electromyographic and pathological features of the Kugelberg-Welander syndrome. In Case 8 there was a later onset of the disease than is usual; but the development of symptoms in adult life has also been reported by other workers.[6] In the patients described in the present study, weakness affected predominantly the proximal muscles of the limb and the muscles of the trunk, but cases have been described elsewhere in which facial or bulbar weakness has occurred.[7,8,9]

In only one of the patients was there a family history of the disease. Both Werdnig-Hoffman disease and Kugelberg-Welander syndrome commonly appear as sporadic cases or with an autosomal recessive mode of inheritance,[2,3,4,5] although an autosomal dominant mode of inheritance has also been described.[10]

The relationship between spinal muscular atrophy of infantile onset (Werdnig-Hoffman disease) and of juvenile or adult onset (Kugelberg-Welander syndrome) is uncertain. Because of the identical pathological natures of the disorders, the similar mode of inheritance in the majority of cases, and the fact that Werdnig-Hoffman disease with prolonged survival cannot readily be distinguished from Kugelberg-Welander syndrome, most authors[6,11] regard the two disorders as clinical variants of the same underlying disease. On the other hand, Buchthal and Olsen[12] have recently emphasized the clinical and electrophysiological differences of the two conditions. Until the nature of the basic underlying defect in the proximal spinal muscular atrophies is discovered, it seems impossible to resolve the matter, or to determine the precise relationship of the spinal muscular atrophies to other diseases such as amyotrophic lateral sclerosis and familial motor neurone disease which are characterized by progressive anterior horn cell degeneration.

Summary

In six of a series of 12 patients with progressive spinal muscular atrophy the onset occurred within the first year of life and the disorder had the characteristic features of infantile spinal muscular atrophy (Werdnig-Hoffman disease). In the remaining six patients the disease, which commenced at a later age and was slowly pro-

gressive, had the clinical, electromyographic and pathological features of juvenile spinal muscular atrophy (Kugelberg-Welander syndrome). The relationship between the two conditions is uncertain but may represent clinical variants of the same underlying disease.

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Werdnig-Hoffmann Syndrome

This syndrome is an unusual progressive atrophy of spinal muscles that occurs in infants. Werdnig and Hoffmann first described this form of infantile paralysis in 1891 and again in 1893. It may be hereditary and familial.

Onset is usually in the first year of life, often in the first six months. Progressive weakness and a gradual development of muscular atrophy are initial symptoms. Involvement includes the muscles of the thigh and deep pelvic girdle, followed by those of the trunk and limbs; and finally the bulbar muscles are involved. There may be fibrillary tremors in the atrophied muscles. A flaccid type of paralysis is seen with little or no reaction of the deep muscle reflexes.

Pathologically, there is degeneration of the anterior roots, of the peripheral nerves, and of the anterior horn cells in the spinal cord. The etiology is not known. Differential diagnosis should exclude amyotonia congenita, which is nonprogressive, does not show complete paralysis, and is accompanied by muscle contractures. Infantile muscular spinal atrophy is always progressive and fatal. Death usually occurs in a few weeks or months, but survival to the age of six years has been reported.

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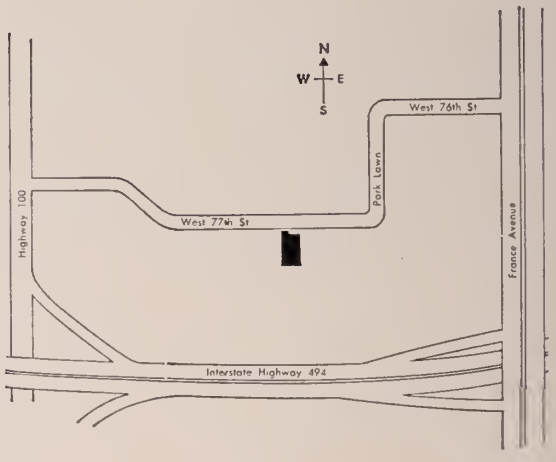
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Advance

Cadaver-Donor Renal Transplantation

Treatment of End-Stage Renal Failure by Dialysis

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ALMOST THREE YEARS ago the Department of Surgery, University of Sydney, working with physicians of the Renal Units of Royal Prince Alfred Hospital and Sydney Hospital and with the staff members of the Tissue Typing group of the New South Wales Red Cross Blood Transfusion Service embarked upon a collaborative enterprise to treat by dialysis and cadaver donor renal transplantation all suitable patients who presented with end stage renal transplantation. The physicians of two other Renal Units, at Concord Repatriation Hospital and St. Vincent's Hospital, supported the effort and more than 20 hospitals agreed to cooperate in allowing access to cadaver donors.

One hundred and forty-one transplantation operations have been performed upon 133 patients since initiation of the scheme and all patients aged up to 56 years who presented have been treated. Information concerning the incidence and causes of end stage renal failure in the Australian community has been gained, and the expectations from this form of treatment have gradually emerged. Progressive improvements in management of patients, tissue matching and immunosuppression are recorded.

Methods

Administrative arrangements allowed the formation of a team of four surgeons and two physicians who had free access to the facilities of two major hospitals to provide a dialysis and transplantation service which operated in both hospitals. The patients maintained by repeated dialysis in these and in the two other hospitals formed a common recipient pool. A further twenty hospitals agreed to cooperate in the procurement of cadaver kidneys.

Recipients

Recipients were aged between eight and 56 years. Only patients with absolute contra-indications to transplantation, such as severe collagen disease or diabetes, strokes, mental disorders or irreversible complications of renal failure, were denied treatment. Dialysis was almost always by haemodialysis, but on some occasions it was necessary to treat some patients temporarily with repeated peritoneal dialysis.

Donors

Only donors who died in hospital were considered. Younger donors were preferred, and it was almost always possible to exclude those with renal abnormalities by renal function tests, microscopic examination of the urine, and intravenous pyelographic examination performed in the ward. Terminally hydration was maintained and, if urine output decreased, diuretics were given. At the time of donor death 50,000 units of heparin were administered. As soon as practical after the death of the donor, both kidneys were removed and perfused with a chilled electrolyte solution. They were then implanted in the iliac fossae of recipients with standard operative techniques.

Tissue Typing

Tissue typing was carried out for all recipients and donors by means of a lymphocytotoxicity test developed from the methods of Walford et al. (1964) and Terasaki et al. (1967). ABO compatible potential recipients were also screened routinely for circulating antibodies which were cytotoxic to lymphocytes of the donor. Two recipients with compatible ABO blood groups, absence of circulating cytotoxic antibodies and with the fewest unshared lymphocyte antigens were chosen to receive the kidneys from each donor.

Immunosuppression

Immunosuppression was with azathioprine, prednisone and Actinomycin C. For the past two years one half of the patients have been treated in a controlled trial with equine antilymphocyte globulin. Episodes of acute rejection were treated with increased prednisone, with Actinomycin C and antilymphocyte globulin, and with systemic anticoagulant therapy.

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#New South Wales Red Cross Blood Transfusion Service.

Other details of donor and recipient selection, surgical procedures, postoperative care and immunosuppression have been presented (Sheil et al., 1968, 1969), as well as details of the controlled clinical trial of the use of anti-lymphocyte globulin (Sheil et al., 1970).

Results

From August 1967, to June 1970, 219 patients with end stage renal failure presented. Twenty-two of these had serious extra-renal disorders which contra-indicated further treatment. One hundred and ninety-seven received dialysis treatment: either haemodialysis (182) or peritoneal dialysis (15). Of these 32 died, 20 in the initial phase of therapy before regular dialysis could be properly established and 12 during the period of regular dialysis. Of the remaining 165 patients three are being treated by home dialysis and 29 by hospital dialysis, either in preparation for or awaiting renal transplantation, and 133 have undergone renal transplantation (Table 1). The causes of renal failure in those patients who received treatment is shown in Table 2.

TABLE 1.

Group	No.
Patients who received renal allografts	133
Patients maintained by dialysis	32
Patients who died during dialysis treatment	
early	20
late	12
Patients not treated because of serious extra-renal disorders	22
Total number	219

TABLE 2.
Causes of End-Stage Renal Failure

Glomerulonephritis	
Chronic	84
Acute	2
Pyelonephritis	43
Analgesic nephropathy	34
Hypertensive nephrosclerosis	10
Polycystic disease	7
Malignant hypertension	4
Miscellaneous	13
	197

For transplantation, kidneys from 92 donors were used. All died in hospital and were aged between five and 57 years, apart from one aged 67 years. With two exceptions, all kidneys were removed and cold perfused within 65 minutes of death of the donor; the exceptional kidneys were from one donor and were removed after 80 and 95 minutes respectively. Apart from four allografts transferred by air from other centres within Australia all were revascularized in the recipient within four hours of death of the donor. The four kidneys transferred by air from other cities were revascularized in four and a quarter hours (twice) and in six and a half hours (twice).

Survival

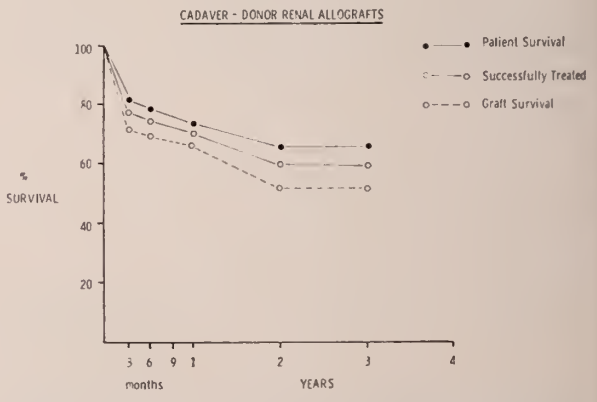
One hundred and forty-one operations were performed upon 133 patients. Seven patients received second grafts following failure of first grafts and one received a third graft. One hundred and two patients (77%) remain alive, 95 (71%) with functioning grafts. Of 76 patients who received grafts from one to three years ago, 52 (68%) survived for one year with functioning grafts, and 50 (66%) continue with functioning grafts (Table 3). The survival of grafts, patients, and successfully treated patients, calculated by the life table method, is shown in the Figure.

Functioning Grafts

Following 141 operations haemodialysis in

TABLE 3.
Results

Total operations	141
Total patients	133
Patients alive	102 (77%)
Patients with functioning grafts	95 (71%)
1 to 3-year survivors	52 (68%)



Figure—Survivals of patients following renal transplantation, of those patients successfully treated, and of grafts are shown.

the postoperative period was not required 109 (77%) times. Of these grafts 81 (74%) still function. Of 32 grafts with delayed function three were virtually non-functional, one because of ABO blood group incompatibility and one because of the early onset of rejection; and one was subsequently found to have ureteric obstruction. Of the remaining 29 grafts with delayed function all subsequently achieved adequate function, but only 14 (44%) still function. In 10 of the grafts which were lost, delayed onset of adequate function following transplantation was felt to play an important part.

Causes of Failure

Of 141 grafts 46 (32%) have ceased function (Table 4).

TABLE 4.
Causes of Graft losses (141 Operations)

	No.	Per cent
Unrelated to operation, rejection or therapy	6	4
Drug toxicity	5	3
Technical	8	6
Rejection	21	15
Ischaemia, rejection and infection	4	3
ABO incompatible	2	1
	46	32%

Unrelated to Operation

The grafts lost because patients died for reasons unrelated to operation, rejection or therapy occurred when patients died of cerebral haemorrhage (twice), cerebral thrombosis (once), myocardial infarction (twice), and complications of an unrelated operation (once).

Drug Toxicity

Five grafts, all functioning well, were lost purely because of drug effects; on three occasions patients died of fungal pneumonia (1), gastrointestinal tract haemorrhage (1) and gastrointestinal tract perforation (1); two other grafts were lost when a patient receiving heparin therapy suffered a severe haemorrhage from the arterial anastomosis and another when therapy was withdrawn from a patient who developed crippling steroid psychosis.

Technical Error

Eight grafts were lost because of technical reasons; ureteric fistulae caused the death of three patients and removal of one graft; late ureteric obstruction occurred on three occasions and in each the graft was removed; one further patient died of pulmonary embolism.

Rejection and Incompatibility

Drug-resistant rejection occurred on 21 occasions; of these, acute rejection occurred within three months of operation 16 times, subacute rejection between three and eight months after operation on four occasions, and chronic rejection one year after operation once. A further four grafts were lost when good renal function was delayed following operation and patients succumbed to infective complications; in all four cases post-mortem histology of the renal allografts revealed the changes of rejection superimposed upon the initial ischaemic insult. Two grafts were lost because of ABO blood group incompatibility; one because of a blood typing error, and the other following an operation undertaken electively early in the programme in the presence of good HL-A matching (Sheil et al., 1969).

Antilymphocyte Globulin

The results of the controlled clinical trial of antilymphocyte globulin therapy have been presented in detail (Sheil et al., 1970). Briefly, toxic side effects of the globulin were not severe, but thrombolytic activity caused thrombocytopenia in one third of the patients on the routine course of therapy and also in others who required increased treatment for rejection episodes. There was no increased incidence of infection in the treated group and no instance of tumour development in either group. For the assessment of immunosuppression in the two groups graft losses due to drug resistant rejection were compared. In the treated group two of 32 grafts were lost because of drug-resistant rejection and no grafts were lost because of rejection and infection. In the control group seven of 32 grafts were lost because of irreversible rejection and a further three because of rejection and infection. The difference in the number of grafts lost in the two groups was significant ($p < .05$). There were also fewer rejection episodes in the treated group and a greater proportion of patients who did not mount a detectable rejection episode within the first three months of transplantation.

Since completion of the trial four months ago a further 10 patients have received globulin therapy without further graft losses because of rejection.

Tissue Matching

Tissue typing was obtained in 139 of 141 operations and results were known before operation 136 times. On two occasions typing was not done and on nine results were considered to be technically unsatisfactory. The results of typing and the present inability to correlate early irreversible rejection with typing have been reported (Stewart et al., 1970).

Discussion

Patients with total renal failure can be treated definitively only be repeated dialysis or by transplantation. With personnel and facilities currently available in Australia the only practical way to treat the large number of young and middle-aged patients without serious contraindications to treatment, is to maintain all patients with irrecoverable renal failure by dialysis and constantly to free dialysis spaces by cadaver donor renal transplantation. In this way it has proved possible to treat all suitable patients who have presented in the past three years, the approximate rate of presentation being 45 per million per year.

Prevention

The causes of renal failure emphasize the importance of prevention in this work and reveal the probability that the number of young patients with renal failure will steadily decrease. In almost half the patients, end stage renal failure might be prevented by more efficient treatment of pyelonephritis, public recognition of the dangers of the abuse of analgesics and effective therapy for hypertension. Increased awareness of the progressive nature of many renal conditions will also result in the patients being referred for therapy at a time when the progress of some diseases can be halted. Earlier referral would also ensure timely dialysis treatment, should this become necessary, which will save many of those patients who are at present desperately ill at the time of their first treatment and who die before regular dialysis can be properly instituted. Nevertheless, the number of patients requiring treatment for end stage renal failure will remain large, as almost one half in this series had glomerulonephritis, the etiology of which remains obscure and the treatment somewhat uncertain. Moreover, the sporadic cases of renal failure cannot be expected to decrease.

Comprehensive care for patients with kidney failure by dialysis and cadaver donor renal transplantation can be provided only by collaboration between hospitals. In this way there is increased access to donor organs and the establishment of large recipient pools; two fundamental requirements in the provision of good-quality, well-matched kidneys for transplantation. However, for such an undertaking to be warranted, cadaver donor renal transplantation must allow survival and rehabilitation of significant numbers of patients. Of those so treated in this series, 77% remain alive, 71% have functioning allografts and 66% have achieved worthwhile prolonged survival. Almost all of the 50 patients with grafts functioning between one and three years following transplantation are satisfactorily rehabilitated and have stable renal function. With continuing advances in immunosuppression, tissue typing and patient management, it is clear that the proportion of successfully treated patients is presently and continuously improving. Even without further improvement the results make continued efforts to treat all those who present mandatory.

Duration of Kidney Survival

The likely duration of the happy period of stable graft function, achieved by the successfully treated recipients in the early years following transplantation, remains undetermined. Except with kidneys from identical twins there is always a low-grade reaction against the allograft and it is generally accepted that all grafts will eventually deteriorate in this process of "chronic rejection." Although some patients from overseas and Australian centres are surviving with cadaver-donor allografts more than five years after transplantation, these survivors from the early days are only a small proportion of those who received transplants then, and the concern is that these patients represent those who have fortuitously received an exceedingly well-matched kidney. However, the long survivors in this series rep-

resent a majority of recipients and, by today's standards, almost all donor-recipient pairs were poorly matched. It is most encouraging that these patients have such stable function and it is possible to say that, even without further advances in typing or immune suppression, cadaver-donor kidney transplantation is abundantly worthwhile. Further, whenever the grafts do fail, be it five, 10 or 15 years after transplantation, there is no reason why the patients cannot receive either second grafts or repeated dialysis, so that further prolonged survival will almost certainly be assured.

One major contribution to the encouraging results presented here is the low incidence of non-function of the allografts. The proportion of non-functioning kidneys in this series was 2.1%, which contrasts with that of 20% reported to the International Transplant Registry (Murray and Barnes, 1968). Only three of 141 kidneys did not produce worthwhile function; one because of ABO blood group incompatibility, one because of the early onset of rejection, and one because of ureteric obstruction. Ischaemia did not cause non-function in any graft, a result consequent upon rigid criteria for donor selection and extensive organization to ensure expeditious removal of kidneys following donor death. Not only has there been a low incidence of non-function but also a high incidence of good early function in the allografts. That prognosis is much improved in the presence of immediate adequate function is apparent, as 73% of those allografts with good early function survive compared with 44% of those with delayed onset of adequate function.

Rejection

By far the most significant cause of graft and patient losses is rejection. Twenty-one (15%) grafts were lost because of drug-resistant rejection, and rejection contributed to the loss of a further eight grafts. However, there is a significant and steady decrease in the number of grafts lost for this reason; 12 of 50 (24%) grafts were irreversibly rejected in our first year's experience and nine of 91 (10%) since. It has not yet been possible to relate this improvement to tissue matching (Stewart et al., 1970). Although we believe that management of donors, recipients and drug therapy has improved progressively and that this has contributed to improving results, this belief is not born out. Rather, the decreased rate of rejection appears to be due to therapy with ALG; of the 91 graft recipients since our first year's experience 49 received treatment with ALG and 42 did not. Graft losses due to drug-resistant rejection in the two groups were 5% and 25% respectively, the latter proportion being almost precisely that of our first year's experience. The conclusion that ALG is exerting a beneficial effect appears inescapable.

The major limitation of the organization has been restricted access to cadaver organs. Although all suitable patients were treated, this was possible only because every donor kidney judged to have recoverable function was used. Although encouraging results are reported, the degrees of tissue compatibility achieved between donors and recipients were far from ideal and there was a significant incidence of delayed function. With free access to cadaveric organs it would be possible invariably to select only those well-matched kidneys which could be expected to function adequately from the time of operation. Thus a high proportion of successfully treated patients would be assured.

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Industrial Medicine

Occupational Medicine in the University of Sydney

G. C. SMITH, M.B., B.S., D.P.H., M.R.A.C.P.*; C. C. REID, M.B., B.S.† and G.J. LINCOLN, B.Sc.‡

University population comprises a large segment of the community. In addition to the administrative, academic and research staff, there are professional and clerical officers, technical and laboratory personnel, tradesmen, labourers, gardeners and other outdoor workers, kitchen and catering staff, miscellaneous employees, and students, both undergraduate and postgraduate.

A university is composed of buildings of various types, ages and sizes used for purposes such as lecture theatres and other teaching rooms; there are also residential colleges, sports areas, gardens and lawns, roadways, and agricultural and animal farms.

Thus, a university is an industry in which several thousands of people with different racial, cultural, social, economic and educational backgrounds and of varying physical and intellectual capacity, are engaged in some kind of work for financial or other type of gain.

Within the working environment of a university there are likely to be hazards to the health or safety of those who work there; problems of toxicology, radiation exposure, noise, ventilation, lighting and accident risk may be encountered. It is not unreasonable to state therefore that a university, especially one of any size, needs an occupational health service or its equivalent.

Many universities do provide a health service which may be primarily established for the benefit of students; or it may be more comprehensive in scope and include dependents of students, academic staff and other employees within the university. Depending on local circumstances, full facilities for prevention and treatment may be provided; or the emphasis may be largely on prevention and the promotion of health and well-being.

Though health service often seems to be a separate entity there should be co-operation between the department of occupational medicine on the one hand and the health service on the other. Indeed the former may well supplement the functions of the latter by undertaking special medical examinations, by advising on possible relationship between health disturbance and work, and by investigating or identifying hazardous or potentially hazardous situations in the environment. A necessary extension of this liaison, especially in a large university, is the establishment of a properly representative safety committee and appointment of a full-time safety officer. The committee should be responsible for implementing the university's policy on safety, in the widest sense of that word.

A department of occupational medicine in a university has a three-fold function, namely, teaching, research and advisory.

The University of Sydney

The University of Sydney employs a salaried and wages staff of nearly 3,200 persons, and its student population, undergraduate and postgraduate, is approximately 16,000. In normal working hours during academic terms thousands of people are within the University area at any one time. Since 1959 the University has maintained a Student Health Service, which is open primarily to all students who wish to seek medical advice on physical and mental health matters. Members of the staff may also consult the Service if they desire.

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Teaching

The Occupational Health Section of the School of Public Health and Tropical Medicine at the University was established in 1948 and is part of the School's Department of Preventive and Social Medicine. The Section has a liaison with the Student Health Service, and both are represented on the University Safety Committee. The Section's physicist is the University Radiation Protection Officer.

In teaching for the University of Sydney, the Section takes part in undergraduate courses in preventive and social medicine, engineering and architecture. At the postgraduate level it participates in the course leading to the Diploma in Public Health and the Diploma in Diagnostic Radiology. It conducts annual courses in occupational health for physicians and for non-medical persons in industry. It also holds periodical courses in ergonomics and assists in the teaching of occupational health nurses. At another university it provides teaching in the undergraduate course in public health and social medicine, and in postgraduate courses in engineering.

Research

Current research projects include studies into the influence of physiotherapy on the progress of occupational cramp, health of manganese miners, occupational associations of ischaemic heart disease, survey of asbestos industries. These investigations all involve industries and occupational groups outside the University, and no research activity directly related to work within the University is at present in progress.

Advisory

The consultative and advisory functions of the Section include health surveillance within the University of certain individuals or groups whose work may expose them to toxic substances or to other hazards and the investigation of environmental problems relevant to health or safety.

On the recommendation of the University Safety Committee, the Vice-Chancellor agreed in 1968 that the Section should survey the activities and potential hazards in laboratories and workshops throughout the University, and some of the Section's activities in health supervision and in environmental investigations are now briefly described.

Health Surveillance

Toxic Substances—General

There are three routes by which toxic substances can enter the body: by ingestion, absorption through the skin, and inhalation of airborne contaminants such as gas, vapour, mist, fume or particulate matter. In the work environment, ingestion of hazardous materials is relatively uncommon and unimportant except for the occasional accident or the would-be suicide. Skin absorption may be sufficient in itself to produce harmful effects or may contribute to those produced by inhalation. Some substances act merely as local irritants at the site of contact with the body skin, the eyes or the respiratory tract; other compounds may be non-irritants but, after absorption into the body, produce systemic poisoning. The toxic compound may be excreted unchanged in the urine, faeces, expired air or sweat; may undergo metabolic changes within the body cells, or may be detoxified by cellular processes, particularly those of the liver.

Poisoning may be acute, subacute or chronic in type. In some cases the rate of absorption of harmful material into the body exceeds the rate of its breakdown or excretion, and a build-up of the toxic compound or its products occurs within that individual, giving rise to a cumulative poisoning.

The most important route of occupational poisoning is by inhalation. Ideally, processes at work should be conducted in such a way that the production of toxic airborne contaminants does not occur; but where achievement of the ideal is not practicable it is essential that inhalation of the contaminant not result in adverse physiological effect, be it injury to a susceptible site in or on the body, or simply reversible discomfort. For all but a few contaminants, reduction of the dose inhaled will, if carried far enough, lead to freedom from adverse effects in almost all exposed workers. The most appropriate method of reducing the dose is to ensure that the concentration of contaminant in the inhaled air not exceed acceptable limits.

The hygienic standards* represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day

*National Health & Medical Research Council of Australia.

without adverse effect. At the same time it is recognized that wide variations exist in individual susceptibility and that a small number of hypersensitive individuals may react at or even below the values listed. The standards should be used only as guides in the control of health hazards and not as dividing lines between safe and dangerous concentrations.

During the working day, the concentration of contaminant in the atmosphere may vary considerably; in most cases the hygienic standards refer to the time-weighted average concentration throughout the work period. However, some fast-acting compounds such as irritants and narcotics are further restricted by the allocation of a ceiling limit value below which all excursions in concentration, other than momentary ones, should be kept.

The Occupational Health Section has been concerned mainly with the problem of possible chronic poisoning or ill health of students or staff of the University from repeated exposure to toxic materials or *ionizing radiation. Traumatic injuries,* which include numerous cuts from handling glassware, burns from corrosive materials or hot objects, and bits from experimental animals, are treated at the Student Health Service or, if the injury is severe, at the local hospital.

Organic Solvents

The health hazard from the use of organic solvents has been not so much acute exposure to high concentrations of solvent vapour as repeated exposure to levels which were not greatly above the recommended hygienic standards. Among undergraduate students, exposure to toxic solvents in the course of class experiments is intermittent and relatively minor, but for some postgraduate students or staff members who use toxic materials essential to their research projects, over a period of several months or even years, there may exist a definite hazard to health unless safe working conditions are maintained.

Benzene is a colourless, very volatile, inflammable liquid with a not unpleasant odour. Its vapour is non-irritating and does not give adequate warning of the presence of hazardous concentrations. Poisoning occurs by the inhalation of the vapour, although some skin absorption also takes place. The main effect of chronic benzene poisoning is upon the blood-forming tissues giving rise to anaemia which may progress to an aplastic type. Changes in the white cell and platelet count may also occur. There have likewise been reports of an increased incidence of leukaemia among persons exposed to benzene.

Carbon tetrachloride does not produce characteristic changes in the blood but may cause kidney or liver damage.

For persons having significant exposure to these solvents routine medical examinations are undertaken at six to twelve monthly intervals, depending upon the degree of exposure. Such examinations include a urinalysis, full blood count, haemoglobin, packed cell volume (microhaematocrit), total and differential white cell count, and study of a blood film for abnormal cells. Routine liver or renal function tests are not performed. The initial examination is made either before or soon after commencing work with the toxic solvent, and the findings, especially the blood count results, form a base line for that individual with which to compare later results. An initial examination is also desirable to detect any pre-existing disorder of the blood or other system which would make it undesirable for that individual to work with these compounds. If the blood count is found to be outside the normal limits, a further examination is carried out in two to four weeks. In most cases it has by then returned to normal. With regular routine blood counts minor variations can be detected by comparison with the previous counts; thus it is hoped to detect any effects of poisoning at an early stage before damage is severe or permanent. While a number of those examined have at times had abnormal blood counts, in all cases these were considered to be unrelated to their solvent exposure; no case of chronic benzene or carbon tetrachloride poisoning has been observed.

When the description of the working conditions suggests that a dangerous concentration of solvent vapour may be present, the area is inspected by both a medical officer and a scientific officer in association with the departmental safety officer. If considered advisable the concentration of solvent vapour in the breathing zone of the worker is determined. Should a dangerous level be detected, advice is given on suitable measures to reduce the ex-

posure.

Other Hazards

Routine medical examinations and blood count estimations are done on some persons exposed to *ionizing radiations,* but the radioactive isotopes and x-ray apparatus used are of such a nature or of such low level of activity as to present little hazard of external radiation. Hence medical examinations and blood counts are not considered necessary for these workers. Those at risk are examined at twelve-month intervals, and none has shown any changes in blood count findings which could be regarded as due to exposure to ionizing radiation. Until the beginning of the year 1970 the Section conducted a film badge monitoring service for radiation workers within the University, but this service has now been taken over by other authorities.

For personnel exposed to *mercury vapour,* mainly arising from spillages of metallic mercury in laboratories, estimations of the amount of mercury excreted in urine have been made. No case of mercury poisoning has been detected, although several years ago raised mercury levels in urine were found among a group employed in a laboratory carrying out blood gas estimations using Van Slyke's apparatus. More modern methods of gas analysis have now largely eliminated the mercury hazard in this laboratory.

Other hazardous materials which were used, but only to a slight extent, included aniline, carbon disulphide, nitrobenzene, tetrachloroethane and carcinogenic amines.

Environmental Studies

During the course of the investigations in laboratories and workshops it became obvious that some personnel had but fragmentary knowledge of the hazardous properties of many of the chemicals frequently used. When attention was drawn to the hazards, certain changes were made in practical exercises for undergraduates; in some cases, it was possible to eliminate the use of hazardous materials from undergraduate laboratories by substituting another chemical of lower toxicity. Where the nature of the task prevented substitution or elimination in undergraduate or research laboratories other precautionary measures were inaugurated.

After several departments had been inspected, the type of information required by the safety officers became evident and a set of safety notes was prepared with sufficient detail to cover the main requirements within the University. In addition to the inspections, services have been made available to carry out analyses in laboratories, workshops and offices where hazardous materials were used.

Mercury

Of the requests for analyses, the most frequent has been concerned with mercury, which is far more toxic than is generally realized. As an indication of the small amount of mercury that may be hazardous, it can be calculated that in order to attain the current recommended hygienic standard of 0.1 mg of vapour per cubic metre of air, the evaporation of only 0.2 microlitres of mercury into 1,000 cubic feet of air is necessary.

Where mercury is used, there will be spillages in spite of precautions and an untreated spillage can constitute a hazard for many years. Repeated treading results in a large number of very small droplets with a large total surface area from which evaporation can occur. Simultaneously, the mercury can be spread on footwear or floor-cleaning equipment to offices, libraries and lunch-rooms, or even further. In one instance, the shoes of an undergraduate were heavily contaminated and a high concentration of vapour was found in his car where droplets were located on the clutch, brake and accelerator pedals. As a second example, vapour was detected at floor level in a laboratory where it was alleged that no mercury had been used for more than 20 years. A shallow drain which was let into the floor and covered by means of a floorboard, had formerly been used to carry waste water from the sinks. On removing the cover, many drops of mercury were discovered, and these were attributed to untreated spillages which had occurred many years previously.

In yet another instance, a large vacuum cleaner had been used to sweep the floors on which mercury had been spilt. When the cleaner was switched on, a very high concentration of mercury vapour was detected in the outgoing air. Drops and vapour had been lifted from the floor by the cleaner, and mercury had deposited inside it. The outflowing air had obviously

been contaminating the atmosphere of offices and other rooms in which it had been used.

Organic Solvents

Other investigations included atmospheric analyses in laboratories in which benzene or carbon tetrachloride have been handled.

In the case of *benzene*, the evaporation of only 2.6 mls into 1,000 cubic feet of air produces the recommended hygienic standard of 25 parts per million (p.p.m.). Analyses of the atmosphere were conducted in a laboratory when the practical exercise involved the bromination of 40 mls of benzene by a class of some 70 undergraduates. By design, the exercise was conducted in such a manner that the benzene was enclosed in all-glass apparatus for most of the time. It was found that the average concentration of vapour in the laboratory was less than 6 p.p.m. with a maximum value of 14 p.p.m., compared with the recommended ceiling limit value of 25 p.p.m. However, some minutes after a spillage had occurred in the service room where the liquid was dispensed from a four-gallon drum, the level reached 720 p.p.m. in the breathing zone of the technician who was filling the smaller containers. This exercise has now been omitted from the course as the result of the hazard arising from bromine and spillages of benzene. In a laboratory where considerable amounts of *carbon tetrachloride* were purified for research purposes, under conditions which were far from ideal but were at the time unavoidable, the atmospheric concentrations of vapour reached some ten times the recommended standard of 10 p.p.m.

Explosion in a Laboratory

A postgraduate research student, whose formal study of chemistry had been limited to one year, was working alone one night to complete some experiments entailing Soxhlet extractions with ether. Having exhausted the supply of solvent in his laboratory, he found a winchester containing sufficient ether for his immediate requirements in a cupboard located in an adjacent laboratory. Being unaware that it had been distilled after an experiment conducted some weeks previously and that no anti-oxidant had been added to the distillate, he poured 150 millilitres into the boiling flask. The concentration of peroxides increased owing to loss of solvent through the condenser and eventually a violent explosion occurred, the student sustaining severe injuries to the face and eyes, requiring surgical treatment.

Miscellaneous

One interesting problem entailed the use of *2-mercaptoethanol* in a buffered aqueous solution required for a research project involving the use of column chromatography and a fraction-collector. The nature of the substances necessitated working in a cold room at 40°F where the air was recirculated and fresh air admitted only when the door was opened, and then to a limited extent. The operator complained of nausea after inhaling the vapour arising from the *mercaptan*. Since it was not practicable to ventilate the cold room and not desirable to propose that a respirator should be worn during research experiments, some other solution was sought. The answer lay in the use of activated charcoal which is highly absorbent at low temperatures. The charcoal was spread on some metal gauze and placed near the effluent of the columns. As a result, the amount of airborne mercaptan was reduced to a level where its odour was not detectable and the operator's symptoms disappeared.

In another department, where blowflies were employed as experimental insects, the insectary was electrically heated during the winter months to a temperature in the vicinity of 75°F. Trouble arose with the electrical circuits in the insectary and re-wiring was necessary. For the purpose, plastic-coated flex was used and, immediately after its installation, the insects died. The cause was traced to *dieldrin* which had been incorporated in the plastic-coated cables during manufacture.

Other requests were related to measurements of the *noise level* in offices, the nature of *odorous emanations* from electronic stencil-cutting machines, precautions required for using micro-organisms in biochemical research and *mutagenic aziridyl compounds*, and disposal of hazardous materials such as *phosgene*, *potassium* and *nitrocellulose*.

Advice has been given to safety personnel on suitable types of respirators and self-contained breathing apparatus for protection of operators using hazardous materials and to

effect a rescue in case of emergency. It is hoped that the latter equipment may be located at suitable places around the University to be readily accessible, yet avoiding the necessity of purchase by every department. Uniformity of type will permit interchangeability of air-cylinders, face-pieces, and other components if required.

The buildings in which the departments are housed vary considerably in age; where necessary, modifications have been made to the older buildings to improve the facilities available to undergraduates and staff. The number of requests for atmospheric analyses or advice has so far shown no correlation with the age of the building.

While details of all the relevant activities of the Occupational Health Section have not been described, it is believed that the subject matter contained herein is sufficient to illustrate the contribution made by the Section to the maintenance of health and safety within the University.

Summary

A university, as a form of industry in which a large segment of the population is engaged in a variety of activities for financial or other type of gain, needs a health service. A department of occupational medicine, in addition to academic commitments in teaching, research and consultation, has an important supplementary role to that of a student or university health service.

Certain groups of persons at special risk, mainly those working with toxic solvents or ionizing radiation, have routine medical and blood count examinations. In association with departmental safety officers hazardous substances and conditions in the working environment are investigated, if necessary by atmospheric sampling, and advice is given on health and safety in laboratories, workshops and other areas of the University.

Two and One Half Billion Heart Beats*

In general, among all groups of organisms sharing a common plan of structure, the large ones live longer than the small. Among plants, the giant sequoia tree lives longer than the daisy. Among animals, the giant sturgeon lives longer than the herring, the giant salamander lives longer than the frog, the giant alligator lives longer than the lizard, the vulture lives longer than the sparrow, and the elephant lives longer than the shrew.

Indeed, in mammals particularly, there seems to be a strong correlation between longevity and size. There are exceptions, to be sure—some startling ones. For instance, whales are extraordinarily short-lived for their size. Most cetaceans are doing very well indeed if they reach 30. This may be because life in the water, with continuous loss of heat and the never-ending necessity of swimming, shortens life.

But much more astonishing is the fact that man has a longer life than any other mammal—much longer than the elephant or even than the closely allied gorilla. When a human centenarian dies, of all the animals in the world alive on the day that he was born, the only ones that remain alive on the day of his death (as far as we know) are a few sluggish turtles, an occasional ancient vulture or sturgeon, and a number of other human centenarians. Not one non-human mammal that came into this world with him has remained. All, without exception (as far as we know), are dead.*

*Isaac Asimov: Of Time and Space and Other Things, 1965.

Special Article

Personal Health Services in Australia

ANTHONY I. ADAMS, M.B., B.S., M.P.H., F.A.P.H.A.*

In her recent overview of the American scene Burns[1] (1969) makes two very significant comments which are entirely pertinent to the organization of medical care in Australia. The first is her observation of "the incredible hodgepodge of our organizational arrangements for the actual delivery of health services," and the second relates to the hospital which "is still too exclusively preoccupied with what goes on within its own walls, to the detriment of the patients, services and practitioners in its community." The aim of this article is to present a cursory comparison between the current Australian and American approaches to the delivery of personal health care, while highlighting a few of the more pressing problems and indicating the progress being made towards their solution.

One of the more obvious differences between the patterns of first contact care in the two countries is that the general practitioner in Australia, despite the declining proportion of graduating students entering general practice, remains the backbone of the health services system. The basic reasons for this are: (1) the Australian community demonstrates a great loyalty to general practitioners, either because of long-term association or because of satisfaction with the services they provide, and (2) the government-supported voluntary health insurance scheme has, since its inception in the early 1950s, deliberately encouraged first contact with general practitioners rather than with specialists. (Insurance rebates on specialists' fees are greater where the patient has been referred by a general practitioner.)

A recent community-based study of a large area of western Sydney, accounting for close to half a million people, indicated that nearly 90 percent of households have a main general practitioner whom they consult on most medical matters. Not only do most of these people state that they are quite satisfied with the quality of the attention they receive from their family doctors, but a significant number feel that they would trust them to carry out abdominal surgery and obstetric care. Some, of course, (and from all indications this is a growing number) are using the public hospital emergency room as a source of primary medical care. This is most pronounced among immigrant groups from Southern Europe who were no doubt more accustomed to seeking help directly from hospitals in their home countries.

No Medically Indigent

Unlike the United States, Australia has no groups in its urban areas readily defined as "medically indigent." General and specialist medical care is almost entirely based on private practice operating on a fee-for-service, and, particularly since recent modifications in the National Health Scheme, no insured member of the public should have financial difficulties in obtaining such care when needed. Persons who pay premiums to one of a number of approved private (non-profit) insurance organizations are entitled to an insurance benefit plus a direct federal government benefit which together meet the cost of most consultations. Under the new legislation no insured person will be out of pocket more than $A5.00† for any consultation or procedure.

In theory this arrangement sounds entirely adequate and the fact that the government subsidizes the insurance scheme ensures that Australians are not overwhelmed with the awesome medical costs that afflict many Americans, however well insured. Yet 15 percent of Australians are not insured and among this group medical costs often cause extreme hardship. The reasons for non-insurance are complex,

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†$A1 = $US1.2

and many feel that compulsory health insurance, along the lines adopted in Canada, for example, would distribute the burden of growing medical costs more equitably over the population. Health insurance is at present a hot political issue.

Group Practice

Whereas the United States has recently witnessed a dramatic increase in group practice, often with arrangements for prepayment, similar developments have been slow to appear here. "Group practice" in Australia still implies the grouping of two or more general practitioners into a single practice with shared facilities and more rational arrangements for out-of-hours care, etc., and for vacations. Only occasionally does one find a group containing one or more specialists, although there can be no doubt that this is the wave of the future. Prepayment schemes based on group practice do not as yet exist, as Americans, familiar with the Kaiser and New York Health Insurance Plans, know them. It is most likely that these will never develop in Australia; the introduction of compulsory and comprehensive tax-supported health insurance is much more probable.

Honorary-Charity

Where general practitioners feel that specialist advice is indicated on an ambulatory basis for their patients, two courses are open. The patient may be referred to a privately-practicing specialist or else to an outpatient clinic of a major public hospital. Patients referred to the latter have tended in the past to be either uninsured or from the lower income groups. Operating on the old charity basis, specialists have given their services free of charge in these clinics, with a means test rigidly applied to patients attending them. This system has become increasingly untenable with the growing affluence of the public and the irrationality of expecting highly skilled professionals to give considerable time to the hospitals without remuneration. Only this year, however, are there signs that the days of the "honorary" system are finally numbered.

Private or State Hospitals

What of the hospitals? The tales of woe concerning the haphazard way in which hospital services developed both in North America and in Australia are well known. In planning for the rationalization and regionalization of health services the heritage of confusion in the quantity and quality of hospitals is one of the major difficulties. In contrast to the United States where the majority of the large hospitals are privately supported, most of the large hospitals in Australia are financed by State governments and are subject to a large degree of public control; hence rationalization of facilities is, theoretically, more readily attainable. However, for reasons relating to the history and prestige of the various hospitals rationalization is not always a welcome concept to their administrators or boards. Furthermore, the large hospitals have tended to remain inward-looking and primarily concerned with the management of acute illness. Few have become concerned with their responsibilities to the community at large, and consequently few provide long-term care for the chronically sick or the aged. These are looked after by a number of private hospitals and nursing homes, many of which are run by religious and other non-profit organizations.

A trend detectable in the last few years has been the establishment of proprietary nursing homes built by private enterprise in areas where, presumably, the profits are going to be greatest. This of course is following a pattern which has been evident in the United States for some time now, a pattern which is to be deplored as it militates against effective quality control in patient care. As in the United States the federal system in Australia has lead to the establishment of some very clumsy arrangements for the financing of health services. Thus, while the acute hospital beds are supported by State money, the chronic hospital beds—fast overtaking the former in number—are financed by the federal government through specific grants (and also through social security pensions which the nursing homes take from the patients) and by the individual patient and his family. (Similarly the problem mentioned above concerning the payment of specialists in outpatient clinics in the major hospitals is confounded by sources of finance. If payment is to be based on fee for service, the federal government—and the insurance companies—will

pay; if on a sessional basis, then the State governments will pay.)

In addition to the privately owned hospitals and nursing homes providing long-term accommodation there are many small private hospitals in the urban areas catering to short-term patients, many of whom require general surgery. In our recent study we were impressed by the finding that nearly a quarter of all admissions took place in such hospitals. Hospital accreditation as known in the United States has yet to be applied to Australian hospitals but will, in all probability, be effected in the near future. Although it will be relatively straightforward to impose standards of excellence on the government-supported hospitals, it may prove exceedingly difficult to make the private hospitals meet these standards. However, the private hospitals must be included in any accreditation programme. (One can envisage the situation in which admission to a recalcitrant hospital no longer qualifies for insurance and government benefit payments, but it is to be hoped that such action can be avoided.) An end to the hospital "hodgepodge" is perhaps in sight with the recent emphasis on the co-ordinated planning of health services based on the concept of regionalization. What is obvious from the above discussion is that, in the absence of planning, hospitals—both public and private—have been sited according to whim rather than to local demand, and the nature of the services they provide has remained geared to the needs of yesteryear.

Regionalization

Regionalization is hardly a new concept, yet in both the U. S. and Australia we talk about it as if it were revolutionary. Observers from countries where regionalization has been a fact of medical life for decades wonder at our tardiness in reorganizing our health services. However, it may be to our advantage to be rethinking our approach to the delivery of medical care at this juncture in order to avoid many of the rigidities that have developed in those countries which have had a completely nationalized health scheme for some time. In the United States regionalization has been discussed for many years but, except for a few specific programmes, regionalization in the fullest sense is far from a reality.

The most exciting concept of regionalization is that in which all health services for a defined population emanate from a regional hospital. It is with this concept that we in Australia are grappling at the present time.

In 1964 Haldeman[2] in the U. S. outlined five main features of a truly regional hospital. This hospital, he said, would become: (1) "as interested in caring for the ambulatory patient as it is now with caring for the bed patient; (2) as concerned with caring for the long-term patient as it is now with caring for the short-term patient; (3) as readily available for assisting the physician with caring for the patient at home as it is now with assisting him in caring for the patient in the hospital; (4) as interested in providing continuity of care for patients in paramedical institutions as it is now with providing continuity of care for patients within the walls of its own buildings; and (5) as dedicated to providing preventive services and teaching health care as it is now in treating the ill."

In the planning of a new public hospital to serve a defined region of western Sydney and to act as one of the teaching hospitals of the University of Sydney, all these features will be incorporated. To co-ordinate the various roles of the hospital as the focal point of all the health services in the region it will have a Department of Community Medicine which will have not only an administrative function but also teaching, research and service responsibilities. It will be staffed by physicians and other professionals with expertise in epidemiology, rehabilitation and geriatric medicine, organization of medical care, multiphasic screening, social work and health education. For Australia this will truly be an experiment, watched closely by hospitals in other areas of Sydney and other parts of the country, to determine whether out of the present "hodgepodge" can be developed a co-ordinated comprehensive system for the delivery of the highest possible quality of health service to a whole population. From what has been said earlier it is obvious that the general practitioner will remain (despite the dismal prophecies of many observers) the major source of first contact care in Australia for some time to come. With wise planning and enlightened negotiation one can foresee the development of a dynamic and

closely knit relationship between the family doctors and their regional hospitals.

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The Race of Life*

Nothing strikes one more in the race of life than to see how many give out in the first half of the course. 'Commencement day' always reminds me of the start for the Derby, when the beautiful high-bred three year-olds of the season are brought up for trial. That day is the start, and life is the race. Some of the best colts are pranced around, a few minutes each, to show their paces. Here we are at Cambridge and a class is first 'graduating.' Poor Harry! he was to have been there, but he has paid forfeit.

Ten years gone. First turn in the race. A few broken down; two or three bolted. 'Cassock,' a black colt, seems to be ahead of the rest. 'Meteor' has pulled up.

Twenty years. Second corner turned. 'Cassock' has dropped from the front, and 'Judex,' an iron-grey, has the lead. But look! how they have thinned out! Down flat—five, six, how many? They will not get up again in this race, be very sure!

Thirty years. Third corner turned. 'Dives,' bright sorrel, ridden by the fellow in a yellow jacket, begins to make play fast—is getting to be the favorite with many. But who is that other one that now shows close up to the front? Don't you remember the quiet brown colt 'Asteroid,' with the star in his forehead? That is he; he is one of the sort that lasts. 'Cassock' is now taking it easily in a gentle trot.

Forty years. More dropping off, but places much as before.

Fifty years. Race over. All that are on the course are coming in at a walk; no more running. Who is ahead? Ahead? What! and the winning-post a slab of white or gray stone standing out from that turf where there is no more jockeying, or straining for victory! Well, the world marks their places in its betting-book; but be sure that these matter very little, if they have run as well as they knew how!*

*Oliver Wendell Holmes (1809-1894)

Wrong Conclusions

America's most popular sport nowadays is not football, baseball, golf, or basketball. It is JUMPING . . . to wrong conclusions about our health! Proof? Over 50% of all the patients consulting us medics each week have NO DIAGNOSABLE PHYSICAL AILMENTS WHATSOEVER!*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

History

The Development of the Medical School at the University of Sydney

RONALD WINTON, M.B., B.S., F.R.A.C.P.*

All medical schools in Australia are an integral part of a university and have been so from their foundation. But although the University of Sydney is the oldest of Australia's universities, its medical school lacks that distinction among Australian medical schools.

The University of Sydney was founded in 1850 but, despite strenuous efforts of various people, it waited for 33 years before its medical school started in 1883. The University of Melbourne was founded in 1853, and only nine years later, in 1862, it began its intake of medical students. In both universities the proponents of a medical school had what they felt was a frustrating struggle to achieve their objective, but the difficulties in Sydney were great, as we shall see. Whether the difficulties were fewer in Melbourne or whether the proponents of a medical school in that city were more persuasive need not delay us here.

The essence of the matter from Sydney's point of view is that for well over half the period from the foundation of the Colony of New South Wales in 1788 to the present day, Sydney had no medical graduates of its own.

Admittedly there were isolated instances of men being granted medical qualifications (Ford, 1955). William Redfern had been transported to Australia in 1801 (13 years after the colony's foundation) for sympathizing with the complaints of the men in the Mutiny at the Nore in 1797, when he was a young assistant surgeon in the Royal Navy. After his arrival in the colony he soon showed the qualities that were to make him in time a distinguished Australian citizen, and in 1803 he was granted an absolute pardon. In 1808 the Lieutenant Governor recommended him for the position of Assistant Surgeon in Sydney, but he had no certificate or diploma of medical qualification. On his offering to submit to an examination in medicine, a Board of Examiners was set up, which satisfied itself of his capabilities and issued him a diploma—the first of its kind in Australia.

In 1813 a young man, James Shears, was apprenticed to Dr. Redfern, only to die in 1814. Then 14-year-old Henry Cowper, son of the Archdeacon of Sydney, became Redfern's apprentice. After three years' apprenticeship and two years as assistant at the new General Hospital, Cowper was pronounced by Redfern to be well trained and efficient. Whether or not he passed a qualifying examination in Sydney is not certain, though it has been inferred (Cowlishaw, 1936) from his appointment as assistant surgeon at the hospital. If so, he was the first young doctor to go from Australia to England for postgraduate study, returning to Sydney in 1823 as (in the terms of an announcement in the *Sydney Gazette* of the day) a Member of the Royal College of Surgeons in London.

Ford also records that Dr. William Bland (another emancipist surgeon) had as an apprentice from 1817 to 1824 an Australian-born lad, William Sherwin who, in his turn, went to England and returned as a Member of the Royal College of Surgeons.

This occasional apprenticeship was all very well, but something more was needed. Though it was not forthcoming for many years, the idea germinated and eventually bore fruit. E. H. Stokes (1960) records that the Medical Practice Bill of 1838 referred to the possibility of a medical school in Sydney, and in 1846 it

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was proposed that a medical school be established at the Sydney Infirmary and Dispensary (later to be renamed Sydney Hospital). Students were admitted to the practice of the Infirmary not later than 1849 and received official recognition from the directors in 1851; "admission was restricted to the articled apprentices and pupils of medical practitioners in the Colony." Frederick Milford, a student admitted in 1849, went to England in 1852 to complete his studies, carrying with him the first official certificate from the President and the Directors of the Infirmary to be presented to one of the examining authorities in England.

Meantime, in 1851, the Royal Assent was given to the Act of Incorporation of the University of Sydney, and in 1852 with three professors (of classics, mathematics, and chemistry and experimental philosophy) and 24 students it commenced to function. In his tribute to the founders of the University at the Centenary Celebrations in 1952, the Chancellor, Sir Charles Blackburn, said: "When they founded the University they did so in the old-fashioned ivory tower with two portals, Arts and Law . . . The next great adventure was when the School of Medicine, the third portal of the ivory tower, was opened." This is a reasonable sequence for the day and age of the University's origins, but the measure of frustration of those who desired a medical school may be gauged from the fact that each of the three dots in the middle of our quotation from the Chancellor's speech represents ten years.

In fact, the Select Report to the Legislative Council relating to the establishment of a university, presented by W. C. Wentworth in 1849, included a recommendation for a chair of anatomy, physiology and medicine (with four others) (Lovell, 1933). The Act of Incorporation of 1850 provided for the granting, after examination, of degrees in Arts, Law and Medicine, and a board of eight examiners was appointed to investigate the qualifications of candidates who had had appropriate medical education elsewhere in the world (four years' attendance at a recognized medical school). But no medical school was in sight, despite the strong support given to the idea by medical men on the University Senate and by Professor John Smith, an Aberdeen medical graduate and occupant of the Chair of Chemistry and Experimental Philosophy. The problem was the familiar one of shortage of funds with competition for what funds were available.

David S. Macmillan, the University Archivist, records (Macmillan, 1958) that in 1859 a scheme of teaching in medicine was adopted, and it was intended to commence these studies in 1860. Edmund Blacket, the University's architect, was instructed by the Senate to prepare plans for an anatomy school; but the classical influence among the professors was strong, and John Woolley, Professor of Classics and Principal of the University, opposed the idea "on the grounds that the constitution of such studies and the establishment of a medical school would retard the completion of the curriculum in the Faculty of Arts." Hence the scheme was dropped.

So was a further scheme in 1866 for the appointment of a professor of anatomy and the building of an anatomy museum. No more successful was an effort led by Professor John Smith and Mr. William Macleay, who bequeathed his museum of natural history to the University in 1874 and who, subsequently, when a medical school did materialize, was one of its major benefactors.

Stokes (1960) makes it clear that when the schemes of 1859 and 1866 were mooted, the University Senate approached the Board of Directors of the Sydney Infirmary for their cooperation, which was readily forthcoming. Detailed plans were worked out, including application to English universities and colleges for recognition of the course, and the 1866 scheme envisaged the spending of two years of the four-year course in London. These schemes, which would have centered the medical school around Sydney Hospital, came to nothing, however. And it is a curious anomaly that when the Sydney University's medical school was eventually founded, a further quarter of a century passed before a clinical school for medical students was inaugurated at Sydney Hospital (as the Infirmary had been renamed).

An incident occurred in 1868 that not only caused a major stir in the Colony but also affected the plans for medical education. H. R. H. Prince Alfred, afterwards the Duke of Edinburgh, was visiting New South Wales, and during a picnic a would-be assassin seriously

wounded him. He recovered, and as a thanks-offering the community raised the sum of £ 30,000 ($60,000). The Duke desired the money to be allocated for the erection of a hospital, Stokes recounts, and at a public meeting held on March 20, 1868, a resolution was carried to the effect that a Prince Alfred Memorial Hospital be erected on the site of the Sydney Infirmary. The Board of the Infirmary was willing but finally had to decline the money because of insuperable legal difficulties relating to the purpose for which the land had been originally allocated.

It was then decided to build the Prince Alfred Memorial Hospital in the vicinity of the University of Sydney. The Act of Parliament providing for the hospital's foundation stipulated that the medical staff of the hospital should be appointed by a conjoint board consisting of the Senate of the University and the Board of Directors of the hospital sitting together, and that it should be open for clinical teaching to students of the medical school when established (Blackburn, 1948). Nine years later, in 1882, the (later Royal) Prince Alfred Hospital opened to receive patients, and in the same year the Government agreed to finance a medical school. Applications were called for for a chair of anatomy and physiology, and Thomas Peter Anderson Stuart came from Edinburgh in Scotland to fill the chair and establish the medical school.

Anderson Stuart was a man of great ability, determination and energy. On the day of his arrival in Sydney in March, 1882, he set to work and toiled unremittingly and effectively in the affairs of his medical school (it was very much his)—as well as in many other worthy causes—until his death in 1920. The medical school of the University of Sydney and its graduates owe far more to him than to any other single individual.

The first medical school building was a four-roomed cottage in the vicinity of the University's Great Hall. It was only partly built when Anderson Stuart arrived in Sydney, but he was undeterred. There were four students waiting to start, and an opening date had been advertised. On that date he delivered the first lectures, despite the absence of windows and doors (some say, also the roof), much to the entertainment (though probably not to the enlightenment) of the workmen.

Sydney's medical faculty grew steadily and surely under the leadership of Anderson Stuart, as Dean and Professor of Anatomy and Physiology. A sound and effective teacher himself, he sought to find men of like mind to help him build up the curriculum. And at the same time he set his heart on a worthy building to house his school.

Understandably he turned for staff to Scotland, and especially to the Edinburgh whose ways he knew and trusted. Among those who responded, and whose names came to be household words in Australian medicine, were Alexander MacCormack, Robert Scot Skirving, J. T. Wilson and D. A. Welsh—Edinburgh men all.

MacCormack and Scot Skirving were early arrivals, in 1883. MacCormack, who was appointed Stuart's demonstrator in anatomy, was a disappointment as a teacher, but he soon achieved great and lasting fame as a surgeon. Skirving was a fine acquisition, both as a clinician and surgeon and as a clinical teacher. Able Australians, such as Philip Sydney Jones and George Rennie, who had been medically educated in England, added their strength, especially in the field of medical teaching. But the Edinburgh tradition was firmly established to the lasting benefit of the Sydney school.

Wilson and Welsh filled new professorial chairs. Wilson became Professor of Anatomy in 1890, so relieving Stuart of part of his responsibility and leaving to him the chair of physiology. Welsh was appointed to a new chair of pathology in 1902. Wilson remained until 1920, establishing a fine reputation, and then returned to Britain to occupy the chair of anatomy at Cambridge, an appointment of considerable distinction. Welsh remained a much loved identity in Sydney's department of pathology until his retirement in 1935.

The curriculum at the beginning, according to S. H. Lovell (1933), covered five years, the first year being spent in the Faculty of Arts. In 1890 the medical course proper was lengthened to five years, the year in Arts being made alternative to a higher matriculation standard. In 1926 it was extended to cover six years. More recently a year of internship has been made obligatory at the end of the under-

graduate six years.

Meantime Anderson Stuart was persisting in his determination to have a building much more fitting than the four-roomed cottage with extensions, and by various skillful and even devious means he succeeded. We need not elaborate on the "means," but in 1887 an ambitious new building was commenced, almost without the University authorities realizing what was happening. The first part was finished by 1891, at a cost of £80,000 ($160,000). Popularly known as "Stuart's Folly," it was considered far too big by most people at the time. But Stuart went on adding to it.

The building, a handsome sandstone structure in Tudor perpendicular Gothic style, known to-day officially as the Anderson Stuart Building, was completed in 1922. It was never too big. "Stuart's Folly" was the dream of a realist, who before his death in 1920 saw substance for his dream. And it was a dream become reality not just in stone, but in teachers, graduates and standards that need be ashamed in no company.

Perhaps the most brilliant of the sons of this school was John Irvine Hunter, who succeeded J. T. Wilson as Professor of Anatomy. With an unparalleled record of achievement as an undergraduate, Hunter was appointed Associate Professor of Anatomy in 1920 at the age of 22, only a few months after his graduation in medicine, and Professor of Anatomy in 1923 at the age of 25. By then he had, according to Hull and Burkitt (1933), established his reputation as one of the foremost anatomists, neurologists and embryologists of his day. In 1924 Hunter and Norman Royle, his co-workers in neurological research, were invited to New York to deliver the John B. Murphy Oration in Surgery. "Hunter delivered his lecture to a crowded audience in the ballroom of the Waldorf Astoria Hotel," Hull and Burkitt record, "and completely dominated that great assembly by his enthusiasm, clarity of exposition, youth, and vitality." Less than two months later he died in London from an acute febrile illness that has never been identified with certainty. Burkitt succeeded him as Professor of Anatomy.

During the 1920s the teaching staff was expanded on the professorial level with a series of new part-time chairs—in medicine and surgery (1920), in psychiatry (1922) and in obstetrics (1925). In 1927 a philanthropic layman, Mr. George H. Bosch, endowed a full-time chair of embryology and histology and, with a further generous gift in 1929, made it possible to establish full-time chairs in bacteriology and (most important of all) in medicine and in surgery.

In 1930 C. G. Lambie came from Scotland to fill the chair of medicine, and a Melbourne surgeon, H. R. Dew, already distinguished for his work on hydatid disease, was appointed to the chair of surgery. In the same year the School of Public Health and Tropical Medicine was founded, with Harvey Sutton as the first professor. The chair of obstetrics became full-time in 1933 and was occupied by J. C. Windeyer.

So by the time of the jubilee of the Sydney University Medical School in 1933, there were full-time chairs in almost all major subjects. These were occupied by men of distinction in their own fields, and with few exceptions they were good teachers. Numbers of students had grown steadily, and despite the world-wide depression of the early 1930s the school was flourishing.

Indeed, it had outgrown Anderson Stuart's building that had been criticised as "too big," and the Univeristy was pleased to accept the offer of the Rockefeller Foundation in New York to provide funds for a new building. This building, carefully planned and situated right beside the Royal Prince Alfred Hospital, was opened to students of the clinical years in the jubilee year of the medical school, leaving Anderson Stuart's building to cater in the main to preclinical subjects.

The Rockefeller-endowed building is today known as the Blackburn Building, in honour of Sir Charles Bickerton Blackburn, who was Dean of the Faculty of Medicine from 1932 to 1935 and Chancellor of the University of Sydney from 1941 to 1964. Though he is now within a few years of his century, Sir Charles is still zestfully active and universally respected.

The most recent structural project is the George H. Bosch Building, which adjoins the Blackburn Building. Its first stage, consisting in the main of four modern, well equipped lecture theatres, was opened in 1967. The

second stage, containing the Dean's office, a fine, much needed medical library, pharmacology laboratories and an animal house, was opened in 1968. The final stage, an 11-story block, is yet to come. When this building and its annexes are completed, at an estimated cost of $6,000,000, the University of Sydney will have a medical precinct second to none in Australia.

With the development of the medical school, and as the growth in the number of students has required it, clinical schools have been begun and built up in Sydney's general and specialist hospitals. Each of these has developed a proud tradition of its own, and most of them today have their own appropriate professorial units, which are still part of the University's medical faculty.

At the same time, with the foundation of a second medical school in Sydney in 1961 at the University of New South Wales, the University of Sydney's medical school organization has had to undergo readjustment. The result has been a sharing both of the load of new medical students and of the hospitals for teaching. This has taken place without undue difficulty, and the two schools now work side by side in harmonious relationship.

An important extension of educational activity, especially during the past quarter of a century, has been the steady growth of postgraduate teaching. This has been in the hands of the University's Postgraduate Committee in Medicine working in close co-operation with the faculty. It has not only helped materially to advance and refresh the knowledge of Australian medical graduates, but has also attracted medical men and women from South East Asia. In this way and through the training of medical undergraduates a useful contribution has been made towards meeting the very real medical needs of our neighbour countries to the north.

Beside the development of the teaching function of the school, which has occupied most of this account, has been the growth, at first slight but latterly rapid and significant, of research in all departments. This has helped to attract and hold able staff members, and has not only resulted in worthwhile research work but also enhanced the quality of teaching and provided a desirable stimulus for the above-average student.

The University of Sydney's medical school is today at an interesting and important stage of development. Deeply in the debt of its founders, who brought to it the insights and the well-tried traditions of an older world, it is now, like the young country to which it belongs, seeking to stand firmly on its own feet and to make its own contribution to contemporary world medicine.

In our modern world, which is at once exciting, challenging and in some ways frightening, the call to Australia seems to be, somewhat paradoxically, to cultivate independence and at the same time to eschew insularity. Towards this ideal the University of Sydney's medical school appears already to have set its face. Ready both to learn from and to contribute to the needs of the world around it, it seeks to make the most of its own resources. To-day almost all its professors and senior faculty members engaged in teaching and research are Australian graduates, and most of them are from the Sydney school itself. This comes not from any cheap spirit of chauvinism, but in the natural way, as a school which has sought to pursue excellence has produced men and women to whom it believes it can confidently entrust the continuance of that pursuit.

Partly because most patients so demand a diagnosis of organic disease, partly because they are inclined to be resentful against the physician who tells them the truth, and partly because it takes so much time and skill and tact to explain the real situation to them, we physicians will always be tempted to dismiss them quickly with some placebo of diagnosis—some pleasant-sounding name such as clitis, ptosis, spastic colon, low blood sugar, or low blood pressure.*

*W. C. Alvarez in Richard MaGraw: Ferment in Medicine, 1966.

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Indications: Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.

Contraindication: Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.

Warnings: Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid, and dosage should be started at a very low level and increased gradually.

Precaution: As with all thyroid preparations this drug will alter results of thyroid function tests.

Adverse Reactions: Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration: Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, T_3 ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.

Instructions for Use: The following conversion table lists the approximate equivalents of other thyroid preparations to Proloid (thyroglobulin) when changing medication from desiccated thyroid, T_4 (sodium levothyroxine), T_3 (sodium liothyronine), or T_4/T_3 (liotrix).

Dose of Proloid (thyroglobulin)	Dose of desiccated thyroid	Dose of T_4 (sodium levothyroxine)	Dose of T_3 (sodium liothyronine)	Dose of liotrix (T_4/T_3)
1 grain	1 grain	0.1 mg	25 mcg	±1 (60 mcg/ 15 mcg)
2 grains	2 grains	0.2 mg	50 mcg	±2 (120 mcg/ 30 mcg)
3 grains	3 grains	0.3 mg	75 mcg	±3 (180 mcg/ 45 mcg)
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.

Overdosage Symptoms: Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

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Books Worth Having

Cancer: Diagnosis, Treatment & Prognosis—*Lauren V. Ackerman & Juan A. del Regato.* C. V. Mosby Co., 1970—Pages 1,049
Illustrations: 783. Price: $39.50

This is an excellent reference for all types of cancer. The illustrations and graphs are pertinent, and at the end of each subject there is an adequate list of bibliographic references. An excellent book.

Psychology of Emotion—*John M. Dorsey, M.D.* Edwards Brothers, Inc., Detroit, Michigan. Price: $6.95. Pages: 174

"Self Discipline by Conscious Emotional Continence" is certainly worth some interesting consideration.

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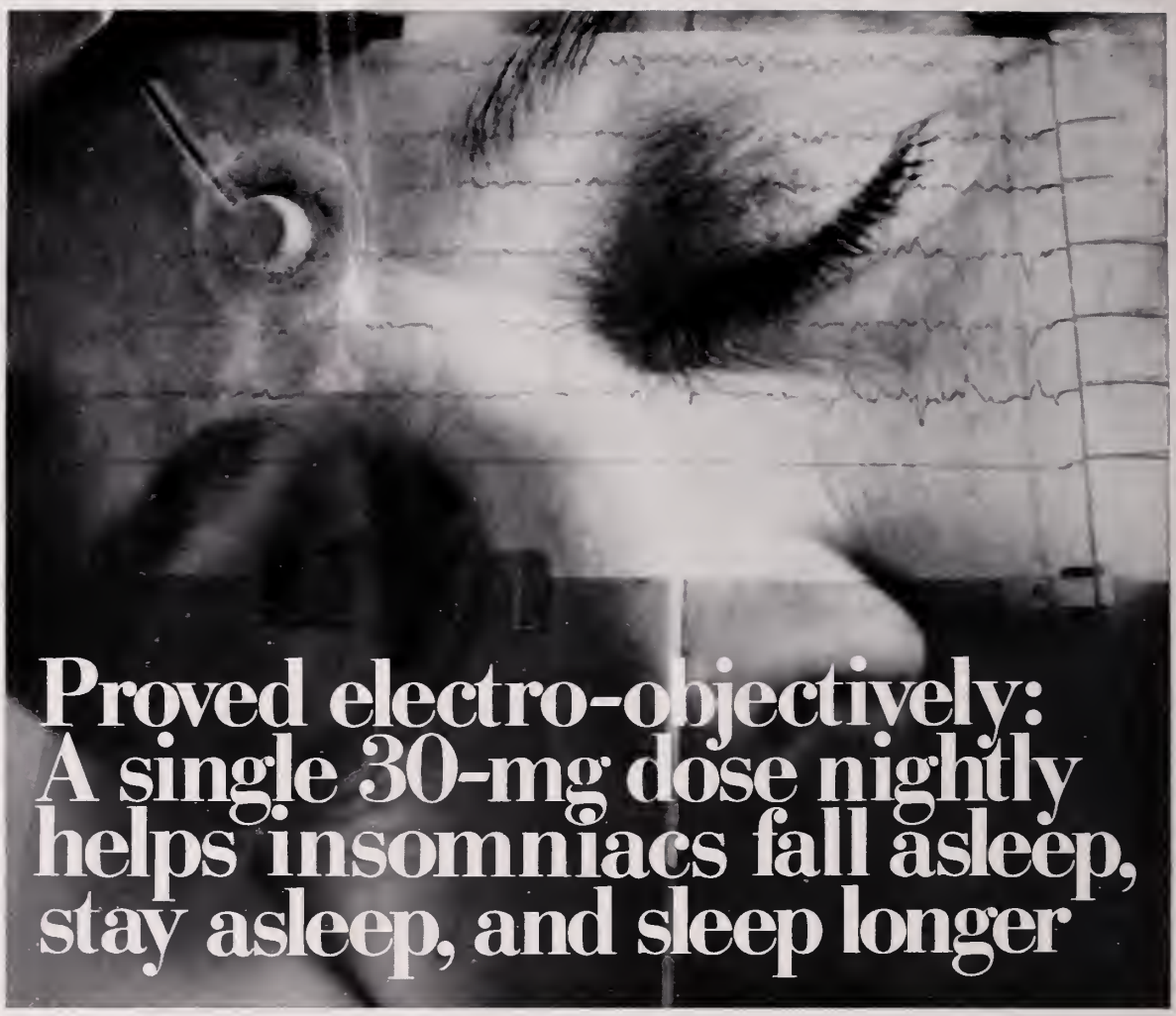
Bruce Linderholm, M.D.

JULY, 1971

Special Issue

Minnesota Urology

Section 1 of Two Sections



Proved electro-objectively: A single 30-mg dose nightly helps insomniacs fall asleep, stay asleep, and sleep longer

Controlled studies of 23 insomniac and 13 normal subjects treated with Dalmane (flurazepam HCl) in five sleep laboratories generated over 4000 hours of electroencephalographic, electro-oculographic and electromyographic tracings. These studies revealed that Dalmane 30 mg nightly usually induces sleep in 22 minutes and provides seven to eight hours of sleep.[1,2,3]

Moreover, Dalmane 30 mg was found to be useful in all common types of insomnia in which it was studied. Of drugs studied in a sleep laboratory,[1] Dalmane 30 mg was the only one that consistently reduced sleep induction time and maintained sleep nightly for 14 consecutive nights of use.

Confirmed clinically

Fifty-three controlled studies using a paired-night, double-blind crossover design have evaluated Dalmane clinically. In the majority of these, Dalmane (flurazepam HCl) significantly reduced sleep induction time and increased sleep duration. Dalmane and a placebo were alternated on successive nights in 2010 insomniacs, 1706 of whom were studied for a single night-pair, and the remainder for as many as fifteen paired-nights. A patient preference for Dalmane was apparent in the paired-night studies.

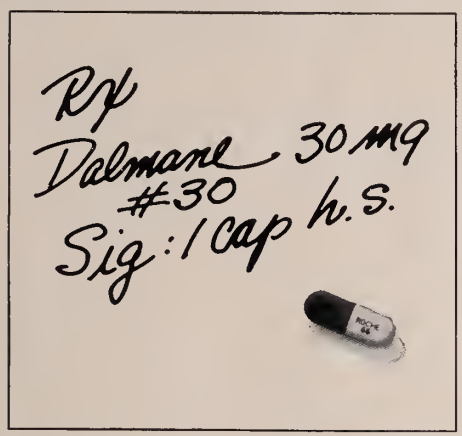
Dalmane was also preferred to certain hypnotics in two separate preference studies. In each of two double-blind studies, Dalmane 30 mg retained effectiveness for the total period of seven consecutive treatment nights, according to subjective/objective evaluations.

In summary, Dalmane is useful in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening. It can be used effectively in patients with recurring insomnia or poor sleeping habits, and in acute or chronic medical situations requiring restful sleep.

Dalmane (flurazepam HCl) is generally well tolerated

In most instances in which adverse effects with Dalmane were reported, they were mild, infrequent and seldom required discontinuation of the drug. Dizziness, drowsiness, lightheadedness and the like were the side effects most frequently noted, particularly in elderly or debilitated patients.[3] Instances of hepatic dysfunction, paradoxical reactions (excitement) and hypotension are rare with Dalmane, and morning hang-over is relatively infrequent. In studies to date the effectiveness of Dalmane for recommended periods of use is maintained without need to increase dosage.

References: 1. Kales, A., *et al.:* "Effectiveness of Sleep Medications: All-Night EEG Studies of Hypnotic Drugs," in Proc. 7th Internat. Cong. Electroencephal. and Clin. Neurophysiol., San Diego, Calif., Sept. 13-19, 1969. **2.** Kales, A., *et al.:* "Psychophysiological and Biochemical Changes Following Use and Withdrawal of Hypnotics," in Kales, A. (ed): *Sleep: Physiology and Pathology*, Phila., Lippincott, 1969, p. 331. **3.** Data on file, Medical Department, Hoffmann-La Roche Inc.



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Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

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Indications: Serious infections due to susceptible strains of *E. coli*, Proteus sp., *Enterobacter aerogenes*, *K. pneumoniae*, *Serratia marcescens* and *Mima-Herellea*. Culture and sensitivity studies should be performed.
Contraindications: A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other agents may be a contraindication if effective alternative therapy is available.
Precautions: Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria) increase hydration and reduce the dosage or the frequency of dosage if necessary – in azotemic patients the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occur, discontinue therapy. Mycotic or bacterial superinfection may occur.
Adverse Reactions: Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.
Dosage and Administration: The maximum total daily dose should not exceed 15 Gm. by all routes of administration. The usual dose is 7.5 mg./Kg./12 hours I.M. The average adult dose is 1 Gm. daily. Uncomplicated infections due to sensitive organisms should respond in 24 to 48 hours.

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President's Letter

Minnesota Urology

Minnesota Urology is alive and well. This observation is supported by the quality of the papers offered in this present issue of *Minnesota Medicine*. However, other lines of evidence lead to the same conclusion.

The quality of urology practiced throughout the state, I believe, is very good. Looking back over the years, we see that the ranks of practicing urologists have been steadily increased by the addition of able and well-trained young men. The Twin City Urologic Society continues to serve not only the urologists of the Twin Cities, but also those from other parts of the state who are able to attend its monthly meetings. These meetings provide an opportunity to share professional experience and information, to keep open lines of communication, and to promote a feeling of fraternity among its members. A visiting professor of national prominence is guest speaker at one of the fall meetings each year.

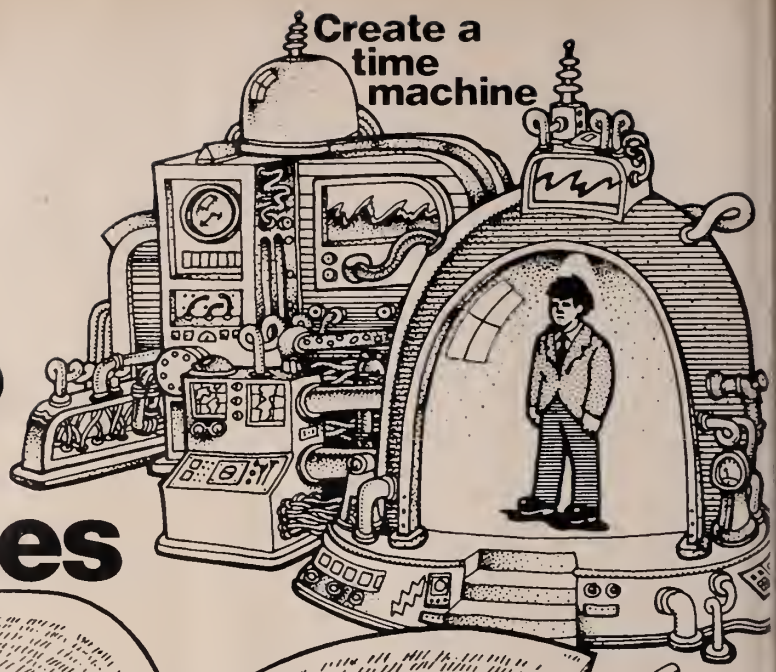
We have every reason to be proud of the training programs in urology offered in our state. At the Mayo Clinic, Dr. Ormond Culp currently heads a program of postgraduate training in urology that has demonstrated its excellence over the years. Dr. Elwin Fraley provides energetic and talented leadership for urologic training at the University and affiliated hospitals, and the very fine residency program at the Minneapolis Veterans Hospital is being ably led by Dr. Clyde Blackard.

However, to say that Minnesota Urology is alive and well without acknowledging our origins would only be self-congratulatory. We simply were not born yesterday, or ten years ago. We were preceded by pioneers of great stature. Dr. William Braasch and Dr. Gershom Thompson were the urology pioneers at the Mayo Clinic. In the Twin Cities, we remember Dr. C. Donald Creevy, Dr. Frederick Foley and Dr. Theodore Sweetser, Sr., as pioneers to whom we looked for wisdom and counsel. Those of us of more ordinary stature have had our vision improved immeasurably by the opportunity of standing on the shoulders of such giants.

It is, therefore, very fitting that the present issue of *Minnesota Medicine* is dedicated to Dr. C. Donald Creevy. But what can we say about a man whose track record of excellence has already earned him national recognition and respect? Dr. Rubin Flocks, Professor of Urology at the University of Iowa, summed it up very well at a recent meeting of the Twin City Urology Society by saying, when asked to comment on Doctor Creevy's presentation on the subject of hypospadias, that we have just listened to a master. We, who have known him for periods varying from a few years to over three decades, will remember that the Professor was always more than a professor. He was, and is, a real Doctor, a real Scholar, a real Man, and in time of need a real Friend. For the privilege of having stood on the shoulders of such a giant we offer our respect and gratitude.

David M. Anderson, M.D., President
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C. Donald Creevy, M.D.

THIS SPECIAL issue is appropriately dedicated to C. Donald Creevy, M. D., Professor Emeritus, formerly Professor of Surgery (Urology) and Director of the Division of Urology at the University of Minnesota.

Throughout his long and distinguished academic career 'Don' Creevy was a colorful and effective teacher of both medical students and house officers. Today, Creevy surrogates are active participants in all phases of American urology, practicing predominantly in the upper midwest. Doctor Creevy's contributions to urology, however, are not restricted to those whom he trained. For example, the discovery by Creevy and his associates that hypotonic irrigating fluids used in transurethral prostatic surgery can cause massive intravascular hemolysis was recognized as a major advance. In addition, his writings, a true reflection of the man, are characterized by a polished epigrammatic style, scholarship and candor.

Although retired from the University since 1967, Dr. Creevy remains active in private practice and resident teaching. His opinions regarding difficult clinical problems are as much sought after today as they were twenty years ago.

Elwin E. Fraley, M.D.*
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Genitourinary Cancers in Minnesota

CLYDE E. BLACKARD, M.D.*

GENITOURINARY CANCERS, excluding the female genital tract, are responsible for approximately 700 deaths annually in the State of Minnesota.[1] Carcinomas of the prostate, bladder, kidney and testis are the leading causes of genitourinary cancer deaths in this State, and in 1968 were responsible for 373, 158, 136 and 17 deaths respectively. When comparing death rates per 100,000 total population, there has been no appreciable reduction in mortality from these four cancers in Minnesota during the past two decades (Table 1). In addition, the death rates from genitourinary cancers in Minnesota in 1967 were higher than those reported for the entire nation (Table 2).[2]

Failure to reduce death rates from genitourinary neoplasms may be due to any one or a combination of the following factors: (1) the increase in life expectancy whereby more people live long enough to develop cancer; (2) an increase in factors causing genitourinary tumors; (3) an increased recognition of advanced genitourinary cancers, and (4) improved reporting of statistics. However, I believe that the main reasons for these surprising statistics are that we have failed in many instances to make an early diagnosis of genitourinary cancers, and often our methods of treatment have been inadequate.

Laboratory and Clinical Research

Both urologists and non-urologists throughout Minnesota have been increasing their efforts to reduce morbidity and mortality from genitourinary cancers. These physicians are recognizing that the best opportunity to treat cancer occurs when the patient is first seen. Also, they are acknowledging the importance of referring patients with complex cancer problems to cancer therapy centers, which conduct extensive laboratory and clinical investigative programs in oncology. Two of the major teaching and research centers in Minnesota with which I am familiar are the University of Minnesota and the Mayo Graduate School of Medicine, and a résumé of their programs is presented.

The University of Minnesota has an active basic research program in both tumor virology and tumor immunology. The relationships between a variety of viruses and genitourinary neoplasms in both man and animals are being investigated; in addition, the immunological characteristics of these tumors are under study. Attempts are being made to develop cell lines from both benign and malignant tissues of the genitourinary tract. In this regard, it has been possible to examine the malignant potential of benign hyperplastic prostatic epithelium in vitro. For example, the neoplastic in-vitro transformation of a cell line derived from benign prostatic epithelium was recently reported.[3] The spontaneously transformed human prostatic cells produced invasive carcinoma when injected into the cheek pouch of immune-suppressed hamsters. Other tissues that have been established in cell culture include renal cell carcinoma, renal adenoma, normal kidney tissue and various bladder tumors. At the Minneapolis Veterans Hospital, serum protein and lipid changes in men receiving various doses of diethylstilbestrol and other estrogens are being studied. Also, histological methods of predicting the biological potential of prostatic carcinoma, employing both light and electron microscopy, are being investigated.

TABLE 1
Death Rates for Selected Types of Genitourinary Cancer
Minnesota Residents, 1950-1968

Year	Death Rate per 100,000 Population			
	Prostate	Bladder	Kidney	Testis
1950	9.8	4.4	3.1	0.6
1960	9.8	4.0	3.5	0.2
1968	10.2	4.2	3.7	0.7

TABLE 2
Death Rates for Selected Types of Genitourinary Cancer
Comparing Minnesota to United States, 1967

Area	Death Rate per 100,000 Population			
	Prostate	Bladder	Kidney	Testis
Minnesota	10.7	4.8	3.7	0.5
United States	8.3	4.3	3.0	0.3

*From the Department of Surgery (Urology), Veterans Administration Hospital, Minneapolis, and the University of Minnesota Hospitals, Minneapolis.

In the area of clinical research, improved surgical techniques for retroperitoneal and ilioinguinal lymphadenectomy are being developed. The University group is participating in a nationwide Renal Cell Carcinoma Cooperative Study, and is evaluating the effects of preoperative radiation for the treatment of hypernephromas. The effects of various chemotherapeutic agents on genitourinary tumors are being studied in conjunction with the Department of Medicine. The Minneapolis Veterans Hospital is the principal contributor to the Veterans Administration Cooperative Urological Research Group (VACURG) Cancer of the Prostate and Bladder Studies. This group recently reported that the decrease in cancer mortality associated with a 5.0 milligram daily dose of diethylstilbestrol was offset by a definite increase in cardiovascular deaths.[4-5] Kuisk and others[6] have developed a method of testicular lymphography in which injection of an indicator dye has been eliminated.

Investigators at the Mayo Clinic are attempting to find the cause of the hepatic dysfunction syndrome, and are studying certain enzymes in patients with hypernephroma. Utilizing the hamster, the effects of endocrine manipulation and immunotherapy on experimental kidney tumors are under study. Upon examination of the thymus gland in patients who have died of renal cell carcinoma, complete depopulation of Hassall's corpuscles was found in younger hypernephroma patients as compared to a similar series of patients with prostatic cancer. Investigators are evaluating different urinary cytologic techniques and are also measuring the distribution of water and electrolytes in dogs with various types of urinary diversion. The nature of certain hormones elaborated in some patients with testicular tumors is currently being studied.

In clinical studies at the Mayo Clinic, various diagnostic procedures such as nephrotomography are being evaluated, as well as pre- and postoperative radiotherapy for hypernephromas. The combination of preoperative radiotherapy and planned cystectomy is being evaluated for the treatment of bladder carcinoma. In patients with carcinoma of the prostate, the effects of estrogen on the cardiovascular system are under study. Hanash and associates,[7] studying necropsy material, concluded that the degree of coronary and aortic atherosclerosis was no worse in prostatic cancer patients taking estrogens than in suitably matched controls. The Mayo Clinic Group has also initiated a prospective study of prostatic cancer, and is evaluating various therapeutic plans.

All of the excnterative procedures for cancers of the pelvic organs are of no avail if there is no consistently satisfactory method of supravesical urinary diversion. Investigators at the St. Paul-Ramsey Department of Urology are currently studying improved methods of urinary diversion following cancer surgery in which the bladder is removed.

Objectives of Special Issue

It is evident that a large number of Minnesota physicians are actively engaged in studies which will provide a better understanding of genitourinary oncology and thereby reduce morbidity and mortality from these cancers. This issue of Minnesota Medicine is devoted entirely to laboratory and clinical studies of neoplasms of the prostate, bladder, kidney and testis conducted largely by Minnesota investigators. Dr. Lino J. Arduino, who has been closely allied with our cancer chemotherapy program at the Minneapolis Veterans Administration Hospital, and Drs. Arthur J. Bischoff and Maxwell Malament, who are members of the Veterans Administration Cooperative Urological Research Group, are the exceptions. The purpose of this issue of Minnesota Medicine is not only to provide information on early diagnosis and proper management, but also to stimulate further interest in studies of genitourinary cancers.

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You can preach a better sermon with your life than with your lips.—Goldsmith

Viruses and Human Cancer*

Evidence for a Viral Etiology of Human Genitourinary Neoplasms

ELWIN E. FRALEY, M.D.†

EVEN THOUGH IT IS well known that viruses cause a variety of malignant tumors in animals, a direct link between viruses and cancer in man has not been established. However, the circumstantial evidence suggesting a relation between viral infection and human malignancy is mounting rapidly, and many scientists believe that the viral etiology of certain human tumors will be proved in the near future.

The purpose of this report is to review important recent developments in the incipient field of human viral oncology with special reference to the possible role of viruses as the cause of urinary tract neoplasms in man.

Evidence for Viral Etiology of Human Tumors

Sarcomas

The classic work of Rous in 1911[1] established a filterable agent associated with naturally-occurring sarcomas of chickens. Subsequent investigation showed a comparable agent responsible for murine sarcomas. Both the avian and murine sarcoma viruses are ribonucleic acid (RNA) viruses and have a similar morphology as seen with the electron microscope.

Recently Morton et al.[2] reported virus particles with fine structure similar to the avian and murine agents in tissue culture cells that were derived from human liposarcomas. Furthermore, antibodies in the serum of the patient from whose tumor the culture originated reacted with cytoplasmic antigens in the original liposarcoma and in cultured liposarcoma cells. Morton et al.[3] previously reported immunological studies indicating that osteogenic sarcomas also have common tumor-specific antigens, a finding suggesting a common etiology, and thus consistent with a viral etiology. Family members and close associates of patients with osteogenic sarcomas have a higher incidence of tumor-specific antibodies than the general population, which also supports an infectious etiology.[3] Finally, Finkel[4] has shown that homogenates from human osteogenic sarcomas produce similar tumors in low incidence when injected into hamsters.

Mammary Cancer

Another tumor similar to its counterpart in man is murine mammary cancer. Two different types of virus have been implicated in mammary cancer in mice: (1) an enveloped RNA virus similar in electron microscopic appearance to myxovirus which is related to the development of spontaneous cancer of the breast in mice, and (2) polyoma virus, a deoxyribonucleic acid (DNA) virus, which produces mammary tumors when injected into newborn mice.[5] The tumors caused by these viruses are morphologically indistinguishable. Further, the microscopic appearance of the murine mammary tumors is similar to that of breast cancer in man. The breast milk of tumor-bearing animals is rich in virus particles.

Virus-like particles have been observed in human cancer of the breast and in the breast milk of tumor-bearing patients with the electron microscope.[6,7] However, the morphology of the viruses is not similar to the mouse mammary tumor virus. The size of the virus-like particle in human breast cancer (15-30 mμ) means that if it were one of the known human viruses it would belong to either RNA picornaviruses or to the DNA picodnaviruses. Recently, at least two different research laboratories working independently have grown human breast cancer in tissue culture, and the tissues in culture contain virus-like particles.

Burkitt Lymphoma

The relation between viruses and avian and murine leukoses and a lymphoproliferative disease

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in chickens (Marek's disease) is also well established. There is likewise some data to suggest that viruses may cause human leukemia and lymphoma. However, the best evidence for a viral etiology of a lymphoproliferative disease in man has been found in Burkitt lymphoma.

Burkitt lymphoma is a neoplastic disease restricted to certain regions of equatorial Africa and is seen most frequently in children between the ages of five and 12 years and infrequently in persons older than 20 years. The distribution of this disease in regions whose climate favors the breeding of mosquitos has suggested that the disease may be caused by an arthropod-born virus.[8]

Burkitt lymphoma cells in culture contain a herpes-like virus.[9] This virus which is not herpes simplex, herpes zoster or cytomegalo-virus is now referred to as the Epstein-Barr virus (EBV). Henle recently demonstrated the infectivity of Epstein-Barr virus for human leukocytes in culture.[10] Almost all patients with Burkitt lymphoma have high antibody titers to Epstein-Barr virus.[11]

Recent seroepidemiologic studies suggest that Epstein-Barr virus may also cause infectious mononucleosis or so-called "glandular fever."[12] The similarity between mononucleosis and malignant lymphoproliferative disorders has long been appreciated by clinicians. Why Epstein-Barr virus produces Burkitt lymphoma in some instances and mononucleosis in others and what the relation of malaria is to Burkitt lymphoma are problems currently under intensive investigation.

Carcinoma of the Cervix

Epidemiological studies have shown that Jewish women have a low incidence of carcinoma of the cervix. Thus it was reasoned that carcinoma of the cervix may be caused by an infectious agent in smegma since the sexual partners of these women are usually circumcised at an early age.

Melnick and co-workers[13] attempted to isolate a virus from the foreskin of 180 uncircumcised young men but were successful in only four cases where there was active *herpes progenitalis*. However, the virus that was isolated was a herpes virus with different antigenic and biologic properties from herpes virus infecting non-genital sites. This virus is now called *herpes hominis type II* or *herpes genitalis*.

Subsequent studies have shown that women with known genital herpes have a higher incidence of cervical dysplasia and carcinoma than the general population;[13,14] they also have a higher incidence of circulating antibodies to *herpes type II* virus than the general population.[13] Rawls et al.[15] recently reported that circulating antibodies to *herpes genitalis* occur in 83 percent of women with invasive carcinoma of the cervix and that these antibodies are present in advance of the development of neoplastic changes in the cervix. Recent investigations have shown that the *herpes type II* virus can produce dysplasia in cervices of newborn mice and sarcomas in newborn hamsters.[16,17] The latter observation, if confirmed, may be extremely important because it is the first direct evidence that a human herpes virus can cause malignant transformation either *in vivo* or *in vitro*.

Other epidimeological facts that support viral etiology of carcinoma of the cervix are: (1) the virtual absence of this disease in nuns and (2) the increased incidence of carcinoma of the cervix in prostitutes, who have many different sexual partners and frequent intercourse.

Viruses and Neoplasms of the Urinary Tract

Virus-Induced Neoplasms in Animals

There are at least two naturally-occurring tumors of the genitourinary tract in animals that probably are caused by viruses, and recently prostatic tumors have been induced in hamsters with SV40, a DNA oncogenic virus.

Adenocarcinoma of the kidney in the frog (Lucke's tumor) is a rare tumor but one that has received much experimental study. In fact, this neoplasm has provided some of the most convincing experimental evidence for the oncogenicity of the herpes-type virus. The data suggesting viral causation for this tumor are as follows: (1) viruses with a morphological appearance consistent with a herpes virus can be seen routinely in the tumor of hibernating frogs;[17] (2) in 1965 Tweedell[18] induced tumors with cell-free extracts derived from virus-containing tumors, and (3) recently Mizell et al.[19] produced tumors by injecting frog embryos (rana pipiens) with zonal centrifuge purified fraction of virus-containing tumors. This latter work also showed that the viruses capable of producing tumors were those with a complete nuclear envelope. Thus there is little doubt that Lucke's tumor is caused by a herpes-type virus.

The chronic administration of diethylstilbestrol

to certain strains of mice produces testicular interstitial cell tumors which can be maintained by serial subcutaneous transplantation in inbred mice. The cytoplasm of the tumor cells contains aggregates of virus particles.[20,21] Morphologically these structures correspond to type A particles comparable to those described in other murine tumors. The significance of these particles has yet to be determined. For example, in other murine tumors the type A particles are not thought to be the oncogenic agents. This is an interesting problem and should be investigated more thoroughly.

In 1966 newborn hamster prostatic tissue was transformed *in vitro* with SV40, an oncogenic virus.[22] The transformed dorsal lobe tissue was injected into adult immune-suppressed hamsters where it produced a rapidly-growing, transplantable epithelioid tumor. These tumors killed their animal hosts with widespread metastases, and tumor-bearing animals had hyperacidphosphatemia. In addition, growth of these tumors could be inhibited with hormones.[23] These experiments showed that an oncogenic virus could produce a malignant prostatic tumor that in many ways resembled carcinoma of the prostate in man. This tumor model was the first experimentally-induced animal tumor resembling human cancer of the prostate; it is being used as a study model for carcinoma of the prostate.

Viruses and Urologic Tumors in Man

Carcinoma of the Prostate

It has been reasoned that if carcinoma of the cervix has a viral etiology, tumors of the lower urinary tract in males may also be a venereal disease. However, comparatively little research has been done in this important area.

Specifically with regard to carcinoma of the prostate, the epidemiological information may be important. First, several investigators have reported a lower incidence of carcinoma of the prostate in Jews.[24] Further, Apt[25] reported that cancer of the prostate was higher in Jews who have undergone considerably more cultural and sexual assimilation in Sweden than in Israel. However, the incidence of cancer of Swedish Jews was still less than that of their countrymen. These data again raise the possibility of a connection between early circumcision and the late development of cancer of the genitourinary tract.

Tannenbaum et al.[26,27] reported the presence of filamentous structures in human cancer of the prostate with the electron microscope that resembled similar inclusions seen in the previously mentioned virus-induced frog kidney tumor. It is now reasonably clear that these filamentous structures are not the oncogenic agent in the frog tumors, and their significance in both Lucke's[2] tumor and human cancer of the prostate has yet to be determined. For example, these structures may be fixation artifacts or non-specific structures that appear in any rapidly-proliferating cells. Several laboratories, including our own, are now working on this problem.

There has been surprisingly little effort to isolate viruses from prostatic tissue or secretions. Based on the investigations in carcinoma of the cervix, one of the prime suspects as an infectious cause for carcinoma of the prostate would be *herpes genitalis*. In this regard, Morriseau et al.[28] recently reported isolating herpes virus from the prostatic secretions of two men with prostatitis. The isolates were tentatively identified as *herpes type II;* but this was not proven.

Thus the evidence linking viruses with cancer of the prostate in man is, at best, tenuous. More work is needed to examine the viral flora of the normal prostate, to examine the association between viruses and prostatitis, and to study the male population at various ages for the presence of circulating viral antibodies. Obviously, these studies might provide a clue to the identity of an oncogenic agent. In addition, research must continue in the laboratory to establish cell lines derived from benign and malignant prostatic tissue for the purpose of isolating viruses. In this regard, some progress is being made. For example, the first long-term cell line derived from prostatic epithelium recently has been reported.[29]

Other Urologic Neoplasms

Again, precious little work has been done to determine whether viruses cause other urologic tumors. One such study was an interesting and provocative paper by the Hellstroms et al. in 1968.[30] They found that neuroblastomas often shared common tumor-specific transplantation antigens and that immunologically competent cells of the tumor patient's mother had circulating antitumor antibodies that cross-reacted not only with tumor cells from her own child but also with

tumors from other children. These studies, if confirmed, have the same significance as the work of Morton and suggest that neuroblastomas have common, tumor-specific antigens and may therefore be caused by an infectious agent. Another study by Shah[31] showed that five of 11 Indian patients with cancer of the bladder had detectable serum virus-neutralizing and (T) antibodies to SV40. The oncogenicity of SV40, a DNA virus, is well established in *in-vitro* systems and, as previously mentioned, it was this virus that transformed embryonic hamster prostatic tissue. Finally, in the laboratory, several investigators have transformed animal kidney tissue with a variety of oncogenic viruses, but the resulting tumors have represented poorly differentiated sarcomas.

Conclusions

Careful analysis of recent progress in the field of viral oncology suggests that certain tumors—leukemia, Burkitt lymphoma, soft tissue sarcomas, mammary cancer and carcinoma of the cervix—are most logically the human tumors that are caused by viruses. This conclusion is based not only upon the clinical studies reported herein but also upon previous basic laboratory investigations that, with the exception of carcinoma of the cervix, have established a viral etiology for similar tumors in animals. Work is just beginning to determine whether there is any solid evidence that human genitourinary neoplasms are caused by viruses. For example, at the University of Minnesota attempts are being made to determine whether there is any immunologic, morphologic or virologic evidence that cancers of the prostate, testicle, bladders and kidney are caused by viruses. In our efforts and in simlar studies elsewhere related to other tumors, a variety of research techniques embracing multiple basic science disciplines including electron microscopy, tumor immunology virology, tissue culture and macromolecular biology are being employed. It is clear that, in every respect, the cost of this research is high but the potential reward great. In fact, the identification of cancer-causing viruses in man would be a landmark in medical history that would inevitably lead to the following: (1) vaccines to prevent cancer; (2) immunologic tests for screening and early diagnosis; and (3) the development of rational immunotherapy for established tumors.

Many problems still remain. For example, if a given virus were found to be frequently associated with a particular neoplasm, how would Koch's postulates be fulfilled? Would attempts be made to prove its oncogenic potential by injecting such a virus into human volunteers? Probably not. An alternate approach would be to innoculate viruses and tumor homogenates into primates; this, in fact, has been done on a large scale at several research centers for many years.[32]

However, the results of this latter program have not, as yet, produced any major breakthroughs. Another approach would be to develop vaccines using the virus or viruses frequently associated with a human neoplasm. If the vaccine uniformly prevented that cancer, it would be presumptive evidence for the oncogenic nature of the virus. This is not an unreasonable approach if one remembers that the vaccination for the prevention of smallpox was done by Jenner before the existence of bacteria was known. In addition, there are several other possible experimental approaches for proving the cancer-causing ability of certain viruses which are now under study. Nevertheless, the task of proving that a given virus causes cancer in man may be most difficult.

In conclusion, emphasis should be given to the fact that viral oncology is one of the most important areas in cancer research. The search for cancer-causing viruses in man is a reasoned and systematic undertaking that has evolved directly from studies in animal tumor systems. Recent clinical studies as reported herein have given added direction to these research efforts.

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How many "coming men" has one known! Where on earth do they all go to?

—Arthur Pinero

Hypernephroma

The New Image

MICHAEL M. WARREN, M.D.;* DAVID C. UTZ, M.D.† and
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Hypernephroma was described by Grawitz[1] in 1883 and frequently bears his name. Little was known about this tumor for many years, and the diagnosis of it was made only in its late stages. The classic triad of gross hematuria, palpable abdominal mass, and flank pain usually was required to alert the examiner to the presence of this lesion, but these symptoms were secondary to gross spread of tumor to involve the renal collecting system or perirenal tissue. Hence, for these patients the prognosis would be grave because the tumor was widespread at the time of initial diagnosis.

Clinicians have learned that hypernephroma may present with other clinical manifestations at an earlier stage. In fact, this neoplasm may cause such a wide variety of nonurinary symptoms that almost every physician, regardless of his field of interest, may encounter patients with symptoms due to hypernephroma but simulating other disease processes.[2] Hypernephroma may be confused with any systemic disease, such as tuberculosis, sarcoidosis, multiple myeloma, amyloidosis, or collagen diseases.[3]

The realization that hypernephroma may present with such a wide variety of symptoms has made possible early diagnosis of this lesion and, hopefully, improved prognosis. Herein we present some of the diagnostic concepts related to hypernephroma and indicate how these have modified the course of the disease.

Current Presentation of Hypernephroma

To determine the current clinical status of hypernephroma and to trace the evolution of its recognition, we reviewed 400 cases of histologically proved hypernephroma treated at the Mayo Clinic from 1961 through 1967. By comparing this experience with that of previous years, we were able to recognize the factors that have resulted in earlier diagnosis of this lesion. We found that 166 (41%) of the patients presented with urinary complaints and 234 (59%) did not. Eighty-two patients (21%) in the latter group had no significant complaints of any kind, while the remaining 152 (38%) had systemic complaints judged to be related to hypernephroma.

The average age of our patients was 58.7 years (range, 15 to 83 years); the male-to-female ratio was approximately 2:1. These age and sex distributions are essentially the same as those previously reported.[4-7] Although the cardinal symptoms of gross hematuria, palpable mass, and flank pain were present in some of our patients (Table 1), they were less frequent than has been reported in earlier studies.[4-7] In fact, the complete classic triad was present in only 20 of our patients (5% of the total group). On the other hand, more patients presented with the nonurologic complaints that now have been recognized to be associated with hypernephroma (Table 2), such as fever, weight loss, anorexia, nausea, vomiting, and generalized fatigue. In addition, many patients with tumor but without symptoms are being identified as a result of appropriate investigation of microhematuria or hypertension.

Fifteen percent of our patients were discovered to have hypernephroma because the renal lesion had already metastasized. Either bone pain or chronic cough, depending on the site of the metastatic lesion, was a frequent initial complaint. Bi-

TABLE 1

Urologic Symptoms of 400 Patients With Hypernephroma

	Patients	
Symptom	No.	%
Hematuria	128	32
Flank pain	96	24
Palpable abdominal mass	146	36
"Classic triad"	20	5

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†Mayo Clinic and Mayo Foundation: Department of Urology, Rochester.

opsy of the metastatic site was often performed prior to the detection of a renal lesion, and the pathologist's report of "metastatic adenocarcinoma consistent with a renal primary" resulted in the proper diagnosis.

TABLE 2
Presenting Systemic Symptoms of 400 Patients With Hypernephroma

Symptom	Patients No.	Patients %
Weight loss	86	22
Anorexia	62	16
Bone (metastatic) pain	58	15
Malaise, fatigue	56	14
Fever	52	13
Cough	25	6
Anemia	26	7
Neurologic	13	3
Vascular	7	2
Gynecologic	6	2

Future Status of Hypernephroma

Three areas of research, evaluating three different idiosyncrasies of hypernephroma, may in time result in our further understanding of this lesion and indeed may unite to provide more solid knowledge of the nature and development of renal cell adenocarcinoma. The association with polycythemia, hypercalcemia, and hepatic dysfunction is neither unusual nor coincidental. While these abnormalities may seem to be separate and unrelated, certain similarities are of interest. If polycythemia, hypercalcemia, or hepatic dysfunction is present preoperatively and the tumor tissue is completely removed, the abnormality should disappear. In fact, serial evaluation of these parameters can be helpful in two ways. Postoperative determinations of blood hemoglobin and serum calcium concentrations and liver function can provide the assurance that all tumor tissue was successfully removed, if the values have returned to normal. In addition, periodic studies in the follow-up period may provide a clue to development of metastatic lesions because, once additional tumor tissue is present, laboratory values that inititally returned to normal may again become abnormal.

Polycythemia

The association of polycythemia and hypernephroma has been recognized for several years.[8] We found increased hemoglobin levels in 19 patients (5% of the total series). Although the etiologic mechanism of the relationship of polycythemia to hypernephroma is not settled, evidence exists that an erythropoietin-like material secreted by the tumor tissue may be responsible for this phenomenon. When the renal tumor is removed, hemoglobin levels usually return to normal and remain so for as long as hormone-producing tumor tissue is absent.

Hypercalcemia

Albright and Reifenstein,[9] in 1948, reported a case of hypernephroma associated with hypercalcemia, in the absence of bone metastasis. Since that time, several additional case reports have been added to the literature.[10] Fifteen of our patients (4%) were found to have hypercalcemia (10.2 to 15.0 mg/100 ml). Since not all patients had serum calcium determinations performed preoperatively, it was our impression that this number would be significantly greater had all patients been tested: these 15 patients actually represent 13% of the 118 patients who had preoperative serum calcium determinations. The majority of patients presented with nonspecific complaints such as anorexia, fatigue, nausea, or vomiting. After removal of the tumor, calcium levels returned to normal in nine patients and remained above normal in six.

We found serial postoperative serum calcium determinations to be useful. If the calcium value returned to normal postoperatively, it was highly probable that all tumor tissue had been removed. If it subsequently increased again, metastatic tumor tissue usually was present. Three of the 15 patients in this group are alive; in all three cases, postoperative serum calcium levels returned to normal and remained so. Those patients whose calcium values subsequently increased again have all died. The etiology of the phenomenon of hypercalcemia in the presence of hypernephroma is obscure. Thomson and Karat[11] reported that extracts of tumor contain a substance immunochemically similar to parathyroid hormone. This would explain the restoration of normal serum calcium levels when tumor tissue is completely removed.

Hepatic Dysfunction Syndrome

Since 1961 a few case reports have appeared describing the association of hypernephroma with abnormalities in liver function, in the absence of hepatic metastasis.[12-15] As in the cases of those

patients with polycythemia or hypercalcemia, these abnormalities also seem related to the presence of tumor tissue. If complete removal of the primary tumor and any discernible metastases is possible, results of liver function tests should return to normal. In reviewing our cases,[16] it was our opinion that this syndrome was present to a greater degree than had been previously recognized; we found 60 patients (15% of the entire series) presenting with evidence of the hepatic dysfunction syndrome. Specifically studied were alkaline phosphatase, prothrombin time, sulfobromophthalein retention, serum electrophoresis (primarily α_2-globulin) and serum bilirubin (Table 3). Abnormal values in at least three tests were required for inclusion in the group. The majority of these patients presented with nonspecific symptoms of fatigue, weight loss, anorexia, nausea, and vomiting. Only 10 described hematuria or flank pain. As in the case of hypercalcemia, not all patients were studied preoperatively with liver function tests, and it is our impression that, if liver function studies had been performed in all patients with suspected hypernephroma, a greater number would have demonstrated this syndrome. It should be noted that none of these patients had liver metastases. We have learned that the presence of hepatic dysfunction does not necessarily represent such metastasis and is therefore not a contraindication to operation.

TABLE 3
Abnormal Liver Function Tests Found Preoperatively in 60 Patients

Test	Patients No.	Patients %
Sulfobromophthalein retention	55	92
Prothrombin time	44	73
α_2-Globulin	43	72
Indirect bilirubin	42	70
Alkaline phosphatase	36	60

Liver function tests were repeated postoperatively in 31 patients. Thirteen of these demonstrated reversal to normal or near-normal levels, and 11 of these patients are alive. Fourteen patients did not demonstrate reversal of liver function tests postoperatively; of the 13 of these successfully traced, only four are alive. Of the remaining nine patients, eight demonstrated widespread local metastasis at the time of operation, making complete excision of the primary tumor impossible.

If results of postoperative tests of liver function return to normal, additional serial determinations on a periodic basis will provide information of prognostic value. In four patients, all dead, postoperative tests gave normal results, and then subsequently abnormal results during the follow-up period; all of these patients eventually demonstrated local spread or distant metastases.

We advocate study of liver function in those patients with nonspecific complaints or with obscure diagnoses, because such abnormalities may indicate a renal tumor. Furthermore, liver function tests should be performed when the diagnosis is known, since serial postoperative determinations may then provide important prognostic information.

At the current time, little is known about the etiology of abnormal liver function associated with hypernephroma. We are currently studying this phenomenon in our laboratory, utilizing tumor extracts from patients with hypernephroma and this syndrome, in an attempt to reproduce the hepatic dysfunction syndrome in animals and to search for abnormalities of lipoprotein.[17] It would be convenient to postulate the production of a hormonal substance by the hypernephroma tissue, as in the cases associated with hypercalcemia or polycythemia, which in turn would produce abnormalties in liver function. No such substance has yet been isolated.

Summary

Changing diagnostic concepts involving hypernephroma have modified the course of the disease. In this review of 400 recent cases of hypernephroma, emphasis is placed on the phenomena of associated polycythemia, hypercalcemia, and hepatic dysfunction.

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Helpful hint to vacation planners: Don't go there; it's crowded.—Changing Times

Historic Hospitals

SISTINE WARD, HOSPITAL OF THE HOLY SPIRIT, ROME



Medieval medical and nursing care were primitive, and persons fortunate enough to have shelters and families were therefore cared for in their own homes. In the country, the feudal lords were responsible for the care of the indigent. The growth of the towns and cities in the late Middle Ages brought a need for hospitals to care for the urban sick poor. These were usually provided by the Church.

The oldest hospital in Rome, the Hospital of the Holy Spirit, was founded in 1198 by Pope Innocent III. In 1478 Pope Sixtus IV added the ward shown here which bears his name, and which is still in use. The scene was photographed in 1968 through a window connecting the ward to the small apartment where the Grand Master of the hospital once lived and through which he could provide day-and-night supervision of patient care.

In the Sack of Rome on May 6, 1527, troops of the Emperor Charles V broke into the hospital and slew all the patients occupying this ward.

Warren L. Kump, M.D.
Minneapolis, Minnesota

Exfoliative Urinary Cytology

A Useful Clinical Tool

CHARLES C. RIFE, M.D.*

In 1864 Sanders first commented on the finding of shreds of neoplastic tissue in the urine. During the next 80 years, many others made similar observations. However, it was not until 1945, when Papanicolaou and Marshall[2] first published their initial investigations on the use of urinary cytology in the diagnosis of genitourinary cancer, that interest in this clinical tool was rekindled.

Since the initial report, numerous articles have appeared in the literature, attempting to determine through clinical observations the role of urinary cytology in the diagnosis of cancer. It was presumed that, because cytology studies were valuable in the diagnosis of pulmonary and female genital-tract malignancies, they should also be of value in the diagnosis of urinary-tract malignancies.

Literature

In 1947 Papanicolaou[3] published the results of his initial experience with urinary cytology and concluded that it was valuable as a diagnostic tool, but only as an adjunct to other means. This finding was supported by the work of Chute and Williams,[4] and Fremont-Smith, Graham, and Meigs.[5] In 1951 Harrison, Botsford, and Tucker[6] reported their experience with urinary cytology in 614 patients. Of these 614, 82 were found to have malignancies: 67 with vesical neoplasms and 15 with lesions of the kidney. All 67 with vesical lesions and 12 of the 15 with renal lesions demonstrated malignant cells in the urine. There were 15 cases of presumed "false-positive" errors in their series (an incidence of 2.4%). It was their conclusion that urinary cytology would be of special value in following patients who had been treated conservatively for tumors of the bladder. McDonald,[7] however, believed that urinary cytology was of questionable value in diagnosing bladder tumors because, in his experience, less than 50% of bladder lesions showed cancer cells in the urine and his "false-positive" reports increased to 8%: figures that were more in agreement with those of previous investigators.

In 1956, a renewed interest in urinary cytology was stimulated by the work of Crabbe et al.,[8] who examined urinary sediments of 1,800 men working in the dyestuff industry. In their series, they noted 67 workers with positive cytologic findings, 51 of whom were found to have bladder tumors on their first cystoscopic examination. Five others, with positive smears, were subsequently found to have bladder neoplasms diagnosed from five months to four years later. Hence they concluded that exfoliative cytology studies were of special value in diagnosing bladder cancers at an early stage, long before symptoms or cystoscopic confirmation could be found. Roland and Marshall[9] reviewed 6,740 smears of 2,414 patients and found that 95% of those with positive smears had cancer. They also pointed out the value of cytologic studies in the early detection of otherwise unsuspected cancer. Foot et al.[10] reviewed the urinary cytologic findings in 2,829 cases and found that 61.7% of the patients with cancers of transitional epithelium origin had demonstrably positive cells in the urine. The incidence of false-positive reports was an impressive 1.2% in their series.

Hazard et al.,[11] in 1957, found an accuracy of 76% and 42 cases of vesical carcinoma. Feeney et al.,[12] however, found only 21 positive smears in 61 proved malignant lesions of the urinary system, but had no false-positive smears. They suggested the possibility of increasing the accuracy of urinary cytology by employing some form of filtering for the concentration of cells. Allegra et al.,[13] in 1966, reported their results in diagnosing

*Mayo Clinic and Mayo Foundation: Department of Urology, Rochester.

occult and in-situ carcinomas of the urinary tract. They successfully diagnosed carcinoma in 108 of the 111 proved cases, with only three false-negative reports; and 13 of their cases showed positive cytologic findings six to 33 months before the tumor could be demonstrated by other methods. They required the presence of cell clumps or tumor fronds before they considered urine as positive for malignant cells. Melamed et al.[14] and Umiker et al.[15] also stressed the importance of exfoliative cytology in detecting bladder cancer in situ, a lesion that Melamed et al.[16] and Utz et al.[17] have pointed out can progress rapidly to an invasive lesion without early cystoscopic evidence.

In 1964 Umiker[18] evaluated the accuracy of the cytologic diagnosis of carcinoma of the bladder in 3,609 cases reported by eight groups of cytologists. This accuracy varied from 26.1 to 100%, with a mean of 71.6%. The incidence of false-positives varied from 1.3 to 11.9%, with a mean of 2.3%.

Technique

Despite the passing of 25 years since Papanicolaou first emphasized urinary cytology as a diagnostic tool, interest in the diagnostic potential of this test has been sporadic and the conclusions have been controversial. The reason for this is due, in part, to the often confusing artifactual alterations that may occur in benign cells when exposed to the hypertonic urine, or in the presence of inflammation or of stones or other nonneoplastic conditions, most of which can be recognized or avoided by the careful attention to the details of urine collection and processing.

Two main techniques are in general use for the cytologic study of urinary exfoliative cytology. The first, and oldest, is the *sediment-smear technique* in which an aliquot of urine is centrifuged and the sediment smeared on a slide. The second, and preferable method in our experience,[19] is the *filtration technique* in which a volume of urine is passed through a transparent membrane with pores of such dimension as to trap (on the membrane) any cells suspended in the urine (Figure A).

Filtration Technique

The second technique allows the collection of cells from a relatively large volume of urine, with a minimum of cellular distortion. Our practice is to collect a freshly voided specimen from the male ("clean-catch" specimen on the female) and, as soon as possible, pass at least 50 ml of the urine through the membrane, utilizing a slight negative pressure. The membrane and trapped cells are then immediately fixed in 95% alcohol and stained later, as convenient. The staining technique is essentially that described by Papanicolaou.

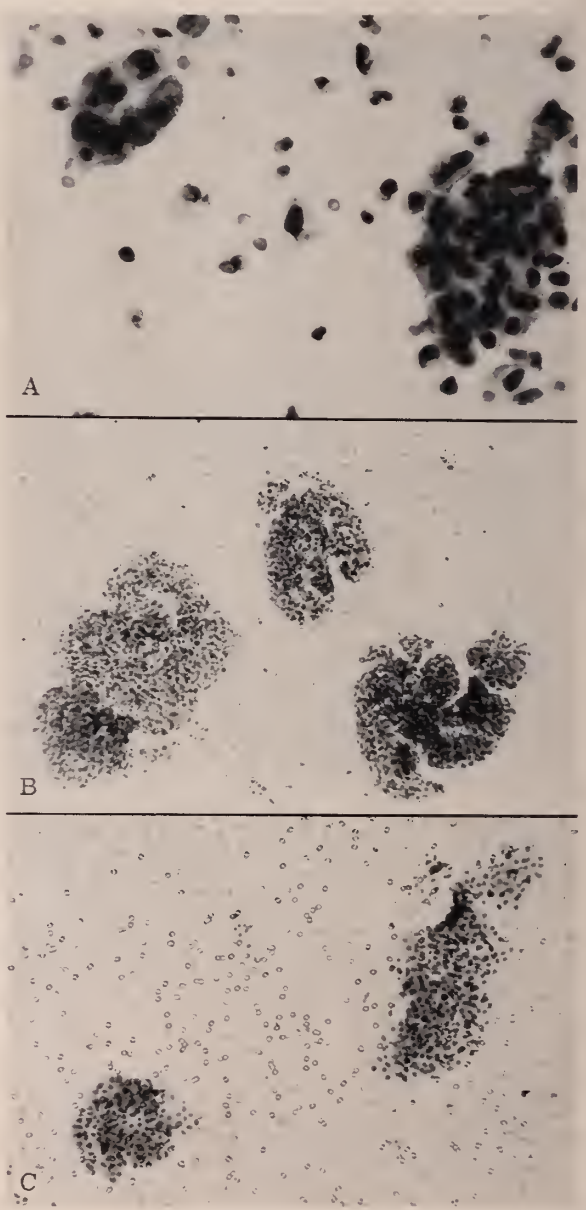


Figure (A) Carcinoma cells of transitional cell carcinoma of bladder trapped on filter. (Papanicolaou; x400.) Figure (B) Voided urine fronds of well-differentiated papillary transitional carcinoma. Note pores in filter, which are 8μ in diameter and appear as clear holes. (Papanicolaou; x90.) Figure (C) These clusters of transitional epithelial cells were induced by instrumentation in absence of neoplasm, and simulated the findings of B. (Papanicolaou; x110.).

Morning Specimine

The least desirable urine for study is the first voided specimen of the morning, because prolonged contact of cells with a hypertonic urine is most likely to produce confusing artifactual changes. Urine collected via catheter or cystoscope, or after any manipulative procedure, is also of somewhat decreased value because of the artificially obtained cell clumps. Normal voided urine in the male contains few epithelial cells and rarely, if ever, clusters or clumps of such cells. The urine of females contains many more single cells but no clumps or clusters. Specimens obtained during or immediately after instrumentation or manipulation contain many more cells than voided urine, and may contain clumps or clusters of epithelial cells displaced from the surface epithelium by the tip of the catheter or instrument. Tumor fronds may be present in voided urine (Figure B), whereas clumps of cells, may be artificially obtained during cystoscopy (Figure C). Such similarity might lead to an erroneous diagnosis of bladder neoplasm.

Exfoliative Oytology

At the present time, we are undertaking an extensive evaluation of exfoliative cytology of the urinary tract in an attempt to ascertain the true value of this tool in a large controlled series. All patients to be examined cystoscopically produce a voided specimen for cytologic evaluation just prior to cystoscopy. Among these patients are those with a history of urinary-tract neoplasms, as well as those with various non-neoplastic urinary-tract disorders. Those with positive cytologic findings are carefully reevaluated until such time as suitable explanation for the cytologic findings can be obtained. Patients with treated neoplasms are reevaluated at intervals by the use of both cytologic and cystoscopic examinations. Though the study is still in its infancy, the value of urinary cytology has already been illustrated many times by the diagnosis of miniscule lesions that previously had defied diagnosis by cystoscopic examination alone. A further report on this study will be forthcoming as soon as a sufficiently large series has been accumulated.

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Two Women

When W. G. Garrison said that for every man who reaches the top of the ladder to success, there is always some woman who stands on the ground and steadies it for him, I would add the phrase "two women": namely, his mother and then his wife.*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

It's the Law

Minnesota Legislature and the Bill for Aid to Minors.

Sections 1 and 2: Emancipated minor or minor who has been married or has borne a child may give consent for medical, mental, dental, or other health services for himself and no other consent is required.

Section 3: Any minor may give effective consent for health services to treat pregnancy and conditions associated therewith, venereal disease, alcohol and other drug abuse, and the consent of no other person is required.

Section 4: Health Services can be given without their parent's consent whenever the risk to the minor's life or health is threatened by delay.

Sections 5 and 6: Physicians who give aid, believing the minor to be emancipated —when indeed he is not—will not be held for assault.

The physician may inform the parent or legal guardian if the life of the minor is threatened.

The minor must assume the financial responsibility.

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Second Engrossment

Sixty-Seventh Session

S. F. NO. 1496

Introduced by Messrs. Gage, Borden, McCutcheon.
Read First Time Mar. 24, 1971 and Referred to the Committee on Judiciary.
Committee Report Adoption, Apr. 22, 1971. To Pass as Amended.
Read Second Time Apr. 22, 1971.
Committee of the Whole Apr. 24, 1971. To Pass as Amended.
Matter in italics is new; matter in capitals when in ( ) is old law to be omitted.

A Bill for an Act Relating to Health: Enabling Certain Minors to Give Effective Consent for Medical, Mental, Dental, and Other Health Services for Himself or His Children.

Be it enacted by the Legislature of the State of Minnesota:

Section 1. Notwithstanding any other provision of law, any minor who is living separate and apart from his parents or legal guardian, whether with or without the consent of a parent or guardian and regardless of the duration of such separate residence, and who is managing his own financial affairs, regardless of the source or extent of his income, may give effective consent to medical, dental, mental and other health services for himself, and the consent of no other person is required.

Section 2. Any minor who has been married or has borne a child may give effective consent to medical, mental, dental and other health services for his or her child, and for himself or herself, and the consent of no other person is required.

Section 3. Any minor may give consent for medical, mental and other health services to determine the presence of or to treat pregnancy and conditions associated therewith, venereal disease, alcohol and other drug abuse, and the consent of no other person is required.

Section 4. Medical, dental, mental and other health services may be rendered to minors of any age without the consent of a parent or legal guardian when, in the professional's judgment, the risk to the minor's life or health is of such a nature that treatment should be given without delay and the requirement of consent would result in delay or denial of treatment.

Section 5. The consent of a minor who represents that he may give effective consent for the purpose of receiving medical, dental, mental or other health services but who may not in fact do so, shall be deemed effective without the consent of the minor's parent or legal guardian, if the person rendering the service relied in good faith upon the representations of the minor.

Section 6. The professional may inform the parent or legal guardian of the minor patient of any treatment given or needed where, in the judgment of the professional, failure to inform the parent or guardian would seriously jeopardize the health of the minor patient.

Section 7. A minor so consenting for such health services shall thereby assume financial responsibility for the cost of said services.

Carcinoma of the Prostate

Clinical Trial Results

THE VETERANS ADMINISTRATION CO-OPERATIVE UROLOGICAL RESEARCH GROUP*

TEN YEARS AGO 14 Veterans Administration hospitals undertook a prospective study to assess properly the standard methods of treatment employed for carcinoma of the prostate.

Method of Study

Estrogen therapy, orchiectomy with a placebo, and a combination of estrogen and orchiectomy were used along with a control drug (placebo). In order to accomplish this end, it was necessary to assign the patients into four categories or stages (Figure 1). No patient with the diagnosis of a second malignant neoplasm, except on skin or lip, was accepted in the study; all patients who had been previously treated for adenocarcinoma of the prostate were excluded.

Radical Plus

In Prostate Study I, 2314 patients were admitted over a period of approximately six and one-half years. All of those in Stages I and II underwent radical prostatectomy; half, chosen by statistical randomization, were given supplementary estrogen and the other half a placebo.

Orchiectomy Plus

For Stages III and IV, in which curability was unlikely, patients were randomly assigned to one of four groups for treatment: namely, estrogen, orchiectomy, plus placebo estrogen plus orchiectomy, or placebo. For all stages and treatment groups, the estrogen employed was 5.0 mg. diethylstilbestrol daily, taken orally. The protocol for this clinical trial, while requiring that the initial treatment be assigned by statistical randomization, nevertheless left the investigator free to change to another treatment later in the study if he felt that the patient's condition demanded it.

It was not the purpose of this trial to simulate a laboratory experiment, but rather to compare the results for general policies of treatment such as one might encounter in clinical practice. In the discussion of results that follows, we will always be referring to the treatments to which the patients were initially assigned.

Stage	Rectal examination	Prostatic acid phosphatase, King-Armstrong units		Roentgenographic or biopsy evidence of metastases
I	No induration	≤1.0		0
II	Localized nodule	≤1.0		0
III	Extraprostatic extension	≤1.0		0
IV	Equivocal findings	>1.0	or	+

Fig. 1—Stage categories used in the Veterans Administration Cooperative Urological Research Group studies of prostatic carcinoma.

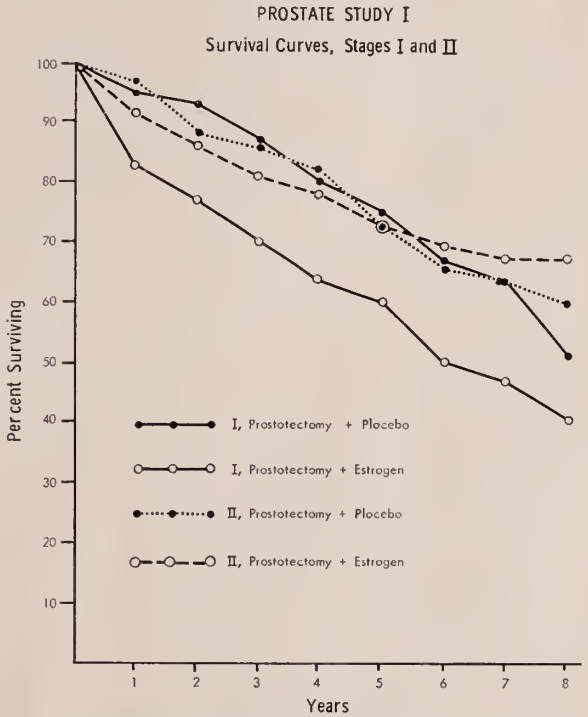


Fig. 2—Survival curves for Stages I and II in the first Veterans Administration study.

*The writing committee consists of Arthur J. Bischoff, Long Beach, California and Maxwell Malament, East Orange, New Jersey.

Members of the group are Lino J. Arduino, Des Moines, Iowa; John C. Bailar, III, Bethesda, Md.; David P. Byar, Bethesda, Md.; Francis F. Bartone, Omaha, Nebr.; Prince D. Beach, Houston, Texas; Leslie E. Becker, Wadsworth, Kansas; Arthur J. Bischoff, Long Beach, Calif.; Clyde E. Blackard, Minneapolis, Minn.; Richard P. Doe, Minneapolis, Minn.; James S. Elliot, Martinez, Calif.; Donald F. Gleason, Minneapolis, Minn..; Earl Haltiwanger, Atlanta, Ga.; Willis P. Jordan, Memphis, Tenn.; Joseph Jorgens, Los Angeles, Calif.; Howard C. Kramer, Fort Howard, Md.; Lyndon E. Lee, Jr., Washington, D.C.; Paul O. Madsen, Madison, Wis.; Maxwell Malament, East Orange, N.J.; George T. Mellinger, Kansas City, Mo.; F. K. Mostofi, Washington, D.C.; William L. Parry, Oklahoma City, Okla.; Raymond Yesner, West Haven, Conn.

Results

The results over an eight-year period showed that placebo plus radical prostatectomy was significantly better than the combination of estrogen and surgery in Stage I. In Stage II there was no statistical difference (Figure 2). The survival curves for Stage III are presented in Figure 3. Placebo and placebo plus orchiectomy are significantly better than estrogen and orchiectomy combined. No other comparisons were significant at any time. In Stage IV patients, there were no statistical differences between any of the treatment methods as far as survival figures were concerned (Figure 4).

It was noted that cardiovascular deaths occurred more frequently in those patients receiving estrogen than in those not treated with estrogen.[2,3] The mechanism of this effect is unknown, but it could be due to changes in the coagulation mechanism or sodium retention or both.

In view of the above findings it was decided to study patients on varying dosages of estrogen in order to determine whether lower doses of diethylstilbestrol might control the cancer without the excess cardiovascular hazard associated with the 5.0 mg. dose.

In Prostate Study II, 508 patients were randomly assigned to one of four treatments: placebo, 0.2 mg. diethylstilbestrol, 1.0 mg. diethylstilbestrol and 5.0 mg. diethylstilbestrol.[4] At the end of 24 months, *preliminary* survival curves in Stage III patients (Figure 5) indicate that individuals who were initially assigned to placebo survived longer than those initially assigned to 5.0 mg. diethylstilbestrol. However, in the Stage IV patients, 1.0

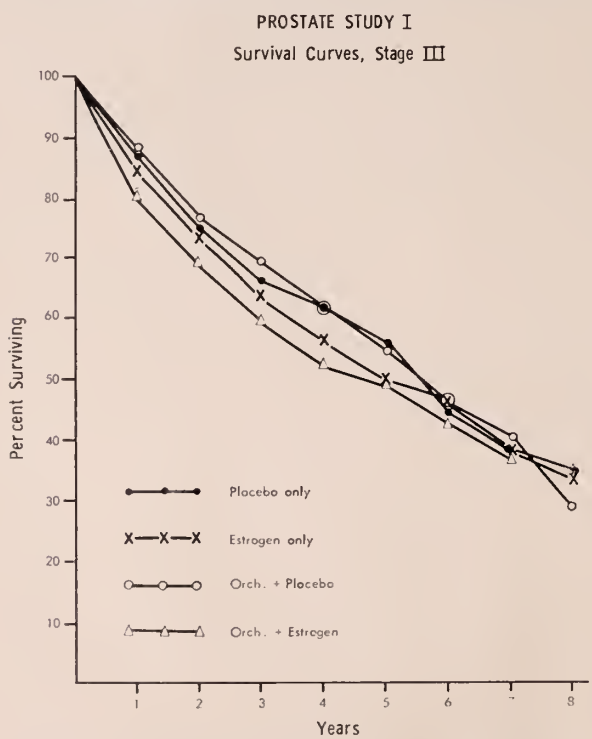


Fig. 3—Survival curves for Stage III in the first Veterans Administration study.

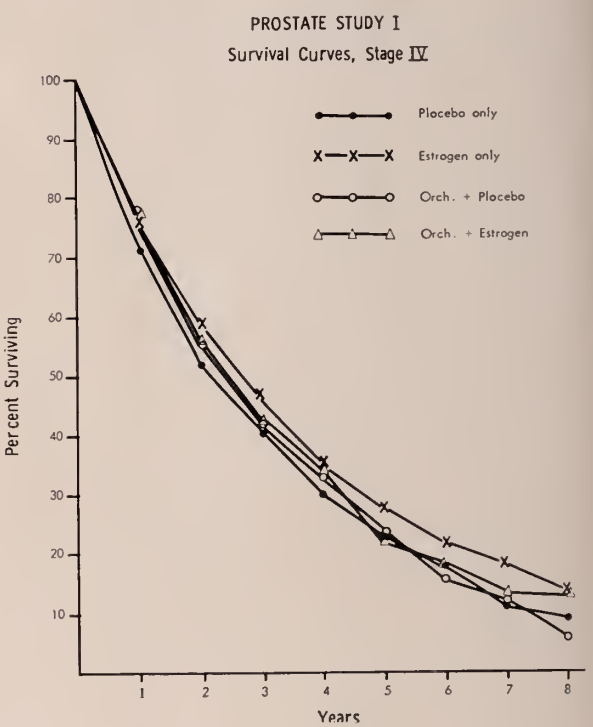


Fig. 4—Survival curves for Stage IV in the first Veterans Administration study.

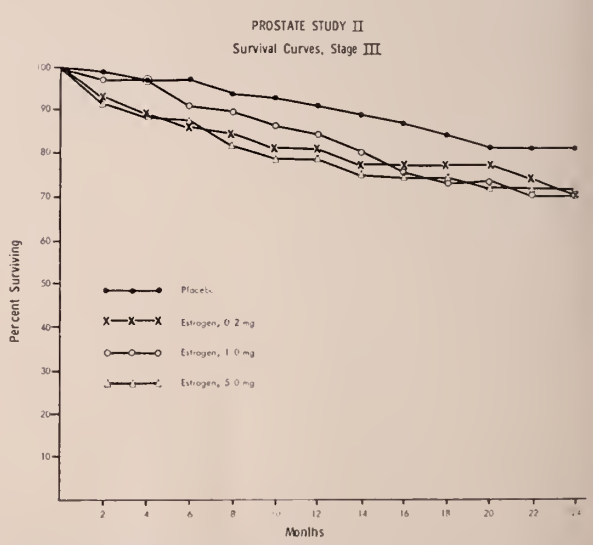


Fig. 5—Survival curves for Stage III in the second Veterans Administration study.

mg. is significantly better than the placebo (Figure 6) and there is no significant difference between 1.0 mg. and 5.0 mg. diethylstilbestrol when cancer deaths only are plotted (not shown in this Figure). Thus, there is no evidence yet that 5.0 mg. diethylstilbestrol is any more effective than 1.0 mg. in reducing deaths from prostatic carcinoma. An analysis of deaths due to cardiovascular causes only (Stages III and IV combined) clearly shows that there is an excess hazard when the 5.0 mg. dosage is employed. Both the curves for placebo and 1.0 mg. diethylstilbestrol differ significantly from that for 5.0 mg. in decreasing the incidence of cardiovascular deaths (Figure 7).

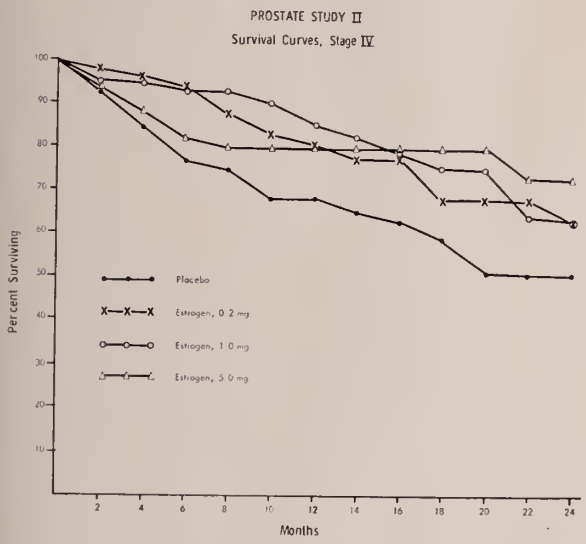


Fig. 6—Survival curves for Stage IV in the second Veterans Administration study.

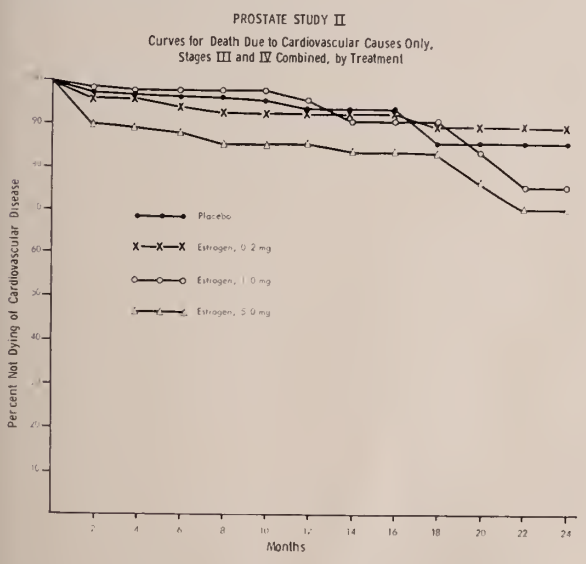


Fig. 7—Actuarial curves for deaths due to cardiovascular causes only for Stage III and IV combined, second Veterans Administration study.

Discussion

The results of the first Veterans Administration study confirmed the long-held clinical impression that both orchiectomy and treatment with 5.0 mg. diethylstilbestrol have a definite if temporary effect on advanced carcinoma of the prostate. It was a great surprise, however, to find that there was a definite excess hazard of cardiovascular deaths among those patients initially assigned to 5.0 mg. diethylstilbestrol, but that the beneficial effects of the drug on the tumor were outweighed by this side effect.

Orchiectomy VS Diethylstilbestrol

It was also a surprise to find that while orchiectomy resulted in some temporary clinical improvement for the patient with advanced disease, this therapy did not increase overall survival whether accompanied by a placebo or by 5.0 mg. diethylstilbestrol. The implication of these findings is that immediate assignment of new patients to either orchiectomy or 5.0 mg. diethylstilbestrol could not be justified in light of our results, since the patients initially assigned to placebo did just as well or better.

The second Veterans Administration study was designed to find out if lower doses of diethylstilbestrol might preserve the beneficial effects on the tumor without the associated excess cardiovascular hazard. It is still too early to make a definitive statement about this, but the results obtained so far indicate that 1.0 mg. diethylstilbestrol is not associated with an excess cardiovascular hazard but that it is as effective as 5.0 mg. in controlling the cancer in Stage IV patients. In Stage III, however, the data indicate that placebo is superior to 5.0 mg. diethylstilbestrol; but even though the survival rates are somewhat higher than those for 0.2 mg. and 1.0 mg., there is no significant difference.

Management Stage III

Taking the results of the two studies together we felt that the best course of action in treating new Stage III patients is to withhold therapy until the acid phosphatase rises above 1.0 KA unit, metastases appear, or the patient's symptoms (pain) demand active therapy. At this time we would recommend the use of 1.0 mg. diethylstilbestrol daily. In Stage IV patients, we recommend starting the patient immediately on 1.0 mg.

For patients in Stages I and II the results from

the first study indicate that radical prostatectomy without supplemental estrogen (at least at 5.0 mg. diethylstilbestrol daily) is the treatment of choice. In the second study we randomized prostatectomy plus placebo with placebo alone to find out whether radical prostatectomy in these early "operable cases" does, in fact, increase survival. It is still too early to comment on this aspect of the study.

We would like to emphasize that these treatment recommendations are somewhat tentative, especially those based on the early results of the second study. All patients in both studies are being followed for 15 years or until death and, as more data are accumulated, the results may change. Also, intensive analysis is currently being directed towards trying to identify those patients for whom estrogen therapy poses excess cardiovascular hazards. Already we have found that patients with a history of cardiovascular disease or with an abnormal EKG fall into this group.[5] In the second Veterans Administration study much additional information about the cardiovascular system has been included, such as blood pressure, EKG, circulation time, cardiothoracic index, and 12 blood studies including fibrinogen, plasminogen, and cholesterol. All these studies are performed every six months at each follow-up visit. We are now beginning to accumulate enough data to initiate a detailed analysis.

In 1969 a third Veterans Administration study was begun. In Stages I and II we are continuing to assign patients randomly to either placebo or placebo plus prostatectomy, and these data will eventually be analyzed along with those from the second study for Stages I and II. In Stages III and IV we are comparing daily doses of 1.0 mg. DES with 2.5 mg. Premarin, 30.0 mg. Provera, and DES plus Provera. It is still too early to comment on this study.

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A Liberal Education

That man, I think, has had a liberal education, who has been so trained in youth that the body is the ready servant of his will, and does with ease and pleasure all the work that, as a mechanism, it is capable of; whose intellect is a clear, cold, logic engine, with all its parts of equal strength, and in smooth working order; ready, like a steam engine, to be turned to any kind of work, and spin the gossamers as well as forge the anchors of the mind; whose mind is stored with a knowledge of the great and fundamental truths of Nature and of the laws of her operations; one who, no stunted ascetic, is full of life and fire, but whose passions are trained to come to heel by a vigorous will, the servant of a tender conscience; who has learned to love all beauty, whether of Nature or of art, to hate all vileness, and to respect others as himself.

Such a one and no other, I conceive, has had a liberal education; for he is, as completely as a man can be, in harmony with Nature. He will make the best of her, and she of him. They will get on together rarely; she as his ever beneficent mother; he as her mouthpiece, her conscious self, her minister and interpreter.*

*Thomas Henry Huxley (1825-1895)

The Scrotal Mass in Young Men

A Diagnostic Dilemma*

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A COMMON PROBLEM for any physician is that of a young man who has recently noticed a lump in his scrotum. Although a careful history is often helpful, physical examination quickly presents the question: "Is this mass malignant?" An immediate answer is necessary because, if the mass is malignant, subsequent treatment with surgery can be life-saving. Though testicular tumors are rare and account for only 1.5 percent of male malignant disease between the ages of 20 to 40 years, they obviously affect young men in the prime of life. It should also be remembered that 97 percent of all testicular tumors are malignant, a rather disturbing statistic (Dixon and Moore, 1952). There is no other malignant disease in the young male for which early treatment can offer so much, if surgery, radiotherapy, and chemotherapy are combined at various stages of the disease. Survival figures with such therapies have constantly improved, so that now even with a radio-resistant tumor such as teratocarcinoma, over 70 percent of patients with combined management have a favorable prognosis.

The role of the primary physician in this disease is critical; the experienced doctor realizes that a wide variety of unusual presentations are possible. Great care must be taken not to be misled by minor injury, alleged strain, or overt infection. The frequently alleged relation of trauma to any testicular mass is well known. Whatever the presentation, every scrotal mass should be treated as a potential cancer until proved otherwise; this is the only way to avoid tragic mistakes. Enlargement due to varicocele, hydrocele, spermatocele, and torsion should always be considered, but one must constantly be aware that it is easy to miss an underlying tumor, particularly in the presence of obvious, coincidental conditions.

A clinical presentation, with a distant metastasis appearing as the first sign, is a tragedy not infrequently seen. Lumbar pain, hemoptysis, abdominal swelling or gynecomastia are typical symptoms, leading to the discovery of previously unsuspected testicular tumor. The primary growth may be minute (1-2 mm.) or even only a chance histological finding.

Perhaps the most difficult clinical problem is the association of the classical signs of epididymitis with a tumor. Again the adage, "a scrotal mass is cancer until proved otherwise," is valuable, for a "pseudo-inflammatory" mass can be the initial presentation in 5 percent of patients (Stephen, 1962).

Examination of the Patient

Physical examination of a scrotal mass is always best made with the patient standing in front of the examiner, and should include a search for distant metastasis by examining the abdomen, liver, and supraclavicular nodes.

When examining the scrotum, the normal testis should be initially inspected, measured, and then used for subsequent comparison. Careful examination should include transillumination, weighing the testes in one's hand, and palpating the different parts of the scrotal contents in a systematic anatomical fashion. Again, when in doubt, the safest rule is to assume a diagnosis of carcinoma until proved otherwise. Never hesitate to seek immediate consultation.

In brief, then, testis tumors have varied and unusual clinical presentations. They require a thoughtful history and examination, coupled with a high index of suspicion that any type of scrotal swelling could be hiding a tumor.

Further Evaluation

Hormone

In addition to a complete clinical evaluation, further laboratory studies of blood, renal function,

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Fig. 1—Chest metastases in a 25-year-old patient with an embryonal cell testicular tumor. Note the large round metastasis in the lower right lobe and the left pleural effusion.



Fig. 2—A preoperative urogram in a 22-year-old man with extensive teratocarcinoma and metastatic retroperitoneal nodes displacing the right ureter laterally.

and urinary hormonal excretion of chorionic gonadotropins should be considered. This latter index study is frequently overlooked but should always be obtained prior to scrotal exploration, because hormonal tests may later serve as a reference point in treatment if the mass proves to be a testicular tumor.

Radiograph

A large "cannon ball metastasis" may be seen in the chest film early in the disease (Figure 1) and lead to a subsequent search for the primary small testicular tumor. Other methods of evaluation should include the intravenous urogram and possible retrograde pyelography and cystography to study the retroperitoneal and related structures. Displacement of the kidney, ureters, or bladder (Figure 2) would suggest involvement of the periaortic and perirenal lymph nodes. Similary, venography may be useful to indicate venacaval obstruction. Lymphangiography can be valuable to show replacement of the lymph nodes by metastatic tumor, and it is of particular importance in diagnosis of testis tumors since their spermatic lymphatics drain directly to the perirenal area, rather than through the inguinal region. Further, lymphangiography is the anatomical basis for subsequent surgical treatment (retroperitoneal lymphadenectomy). Though it has some limitations with false negative findings, it is a useful adjuvant, particularly to confirm the efficiency of a lymph node dissection (Fraley et al., 1965).

The Inguinal Exploration

Technical Points

When a scrotal mass is seen, immediate surgical exploration should be considered if there is the slightest question of a tumor. A high inguinal orchidectomy or scrotal exploration is best performed through the familiar inguinal herniorrhaphy incision. The external oblique aponeurosis is divided laterally from the external ring to reveal the spermatic cord coursing through the inguinal canal. In these often youthful patients, the well formed conjoint tendon arches over the spermatic cord covering the internal inguinal ring. This tendon is retracted or divided to expose the spermatic cord at the internal inguinal ring. Then the cord is gently clamped with two rubber-shod clamps. Blunt and sharp dissection down into the scrotum along the tissue plane below the external spermatic fascia will usually allow easy delivery

of the testicular mass into the inguinal incision with the covering coats intact. In most cases, inspection and palpation may show the hard unmistakable feeling of a malignant testis tumor. The cord should then be transfixed and ligated just proximal to the rubber-shod clamps, identifying and ligating the veins, artery, and ductus deferens separately as part of a meticulous dissection. These structures are next divided. Some surgeons then cauterize the stump. In an unusual case where a small tumor, hematoma, or other disease confuses easy closed identification of the testicular lesion, the wound may have to be carefully packed and the testis and its coverings opened well away from the operative field. Usually, direct inspection of the testes can decide the issue, and orchidectomy can be performed as necessary.

Cancerocidal Fluid

If naked eye inspection is unsatisfactory, frozen section biopsy may be necessary. If any doubt still remains, it is wise to perform the orchidectomy. Replacing a malignant tumor into the scrotum would be injudicious. Fortunately, such a dilemma is rare. If it does occur there should be no hesitation in removing a questionable lesion, guided by clinical judgment, particularly with a normal testis on the other side. Finally, the wound can be irrigated with cancerocidal fluids such as concentrated Furacin.[R]

This approach to testicular masses is important because they are so malignant, with the ever present risk of seeding into adjacent tissues. For example, Dean, in 1925, noted that when performing an amputation of the testis, if the covering was punctured and any of the contents had escaped, a local recurrence was almost certain to follow. In 63 patients seen by him, 65 percent had had a simple transcrotal orchidectomy. Of these, 24 percent had a local recurrence, usually in the first month after the initial treatment.

A similar danger of local implantation may occur if there is any attempt to tap a coincident hydrocele or perform a local needle biopsy. Stephen (1962) mentioned local recurrence following such procedures.

In five consecutive cases referred to the University of Minnesota since 1965, inadequate initial treatment with the risk of tumor implantation had occurred. Initial treatment had included: (1) local biopsy through a transcrotal incision, (2) removal of the testis, but preservation of the surrounding tunics, (3) removal of the testis and the epididymis, leaving the spermatic cord, (4) transcrotal needle biopsy and (5) problems with an infected spermatic cord stump following a transcrotal orchidectomy.

[R]Furacin Solution. Eaton Laboratories, New York.

Case Reports

Case 1

A 33-year-old man with testicular teratocarcinoma was initially seen with massive inguinal and spermatic cord metastases three weeks after local scrotal orchidectomy. The cord and its coverings had been left behind with tunica vaginalis. Biopsy confirmed a tumor penetrating a new lymphatic drainage area, the superficial and deep inguinal nodes (Figure 3).

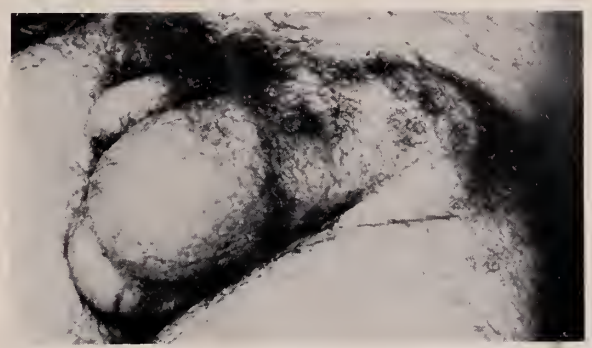


Fig. 3—'Contaminated' orchidectomy. Note the massive spermatic and inguinal nodes following a transcrotal orchidectomy three weeks previously for teratocarcinoma of the testis.

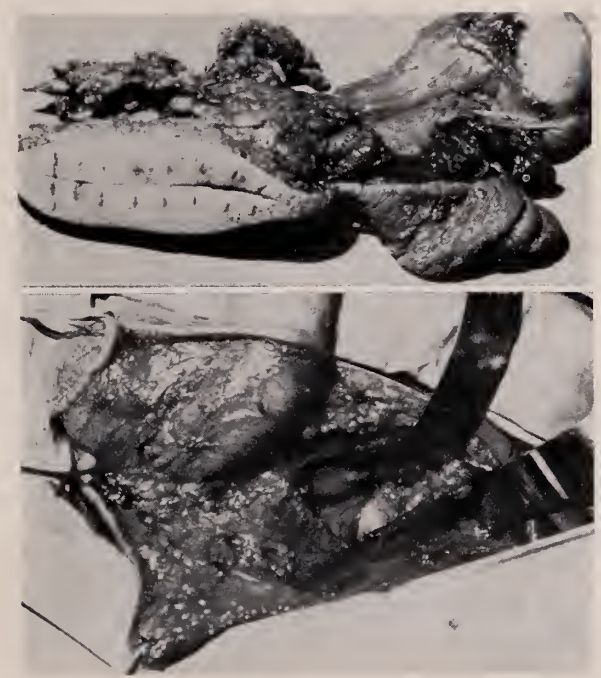


Fig. 4—Contaminated orchidectomy (top) The specimen from an 'en bloc' dissection includes the previously biopsied testis, the hemiscrotectomy and adjacent inguinal nodes; with (Bottom) the extensive inguinal exposure.

Case 2

A 20-year-old doctor's son was seen following simple orchidectomy for embryonal cell cancer. Though the testis was carefully removed through an inguinal incision the tunica vaginalis was then closed and returned to the scrotum. When referred for further treatment, even though there were no inguinal nodes, a residual smooth mass of tunica vaginalis, cord and hematoma was found, which felt like the original testis. As this raised the question of recurrent tumor or inadequate primary surgery, radical hemiscrotectomy and 'en bloc' groin dissection were performed (Figure 4).

Case 3

A 22-year-old farmer underwent transcrotal biopsy of an epididymal disease. Subsequent hemiscrotectomy and inguinal 'en bloc' dissection confirmed residual embryonal cell tumor of the testis.

Treatment of Local Implantation

Inguinal excision and hemiscrotectomy were combined with 'en bloc' ipsilateral radical inguinal groin dissection in four of five patients. There has been no recurrence in the four who were treated by subsequent more distal radical thoracoabdominal lymphadenectomy. Stephen (1962) reported performing hemiscrotectomy on four patients seen under these circumstances. Leadbetter (1967) recommended immediate hemiscrotectomy with wide excision of the inguinal lymph nodes.

If transgression of a tumor-bearing area or inadequate surgical excision has occurred during the initial exploration, 'en bloc' radical lymph node dissection may be necessary to include the local lymphatics and surrounding local tissue.

Subsequent Treatment

Further treatment depends upon the type and clinical stage of the disease. To prevent local recurrence, seminoma is treated using radiotherapy, and choriocarcinoma is treated with chemotherapy. Radioresistant embryonal and teratocarcinoma are best handled by radical lymphadenectomy to remove areas of potential lymphatic spread.

References may be secured from the author or the reprints.

Discussion

These experiences with the management of the "contaminated orchidectomy" emphasizes the importance of accurate preoperative clinical assessment and initial surgical care. An improper early assessment can compromise the primary cancer operation and subsequent treatment. Needling, trocar punches, local biopsy, transcrotal exploration, simple or partial orchidectomy may appear easier and simpler methods of obtaining information about a scrotal mass but can result in tumor spread into a previously uncontaminated lymphatic drainage area. Inguinal exposure of the scrotal mass, although involving more dissection, is the correct surgical approach for scrotal masses.

A review of reported major series of testicular tumors over the last 20 years (Markland 1968) repeatedly showed that delay in seeking treatment was a common and tragic problem. Subsequent misdiagnosis was common and emphasized the fact that the disease was often indistinguishable from acute infection, hematoma, and associated conditions. An answer to these problems must depend on increased awareness of the problem by both the patient and the doctor. It would be worthwhile to encourage self-examination of the testes in men, similar to the self-examination stressed in the detection of breast cancer. Such a public campaign might result in increased awareness and suspicion of testicular cancer. Continued recognition of the difficulties posed by all scrotal masses is a responsibility shared by every physician.

In general then, improvement in the management of these problems depends upon accurate initial diagnosis and the prompt institution of correct treatment. This decision, particularly when dealing with teratomatous tumors, is often complicated and will depend upon the availability of radiotherapy and chemotherapy, together with specialized types of surgery. Though testicular tumors are rare, the role of the primary physician is critical, justifying the continuing attitude that all scrotal masses are cancer, until proved otherwise.

When Taft once went bathing in Beverly Bay, a neighbor said, "I'd like to go in for a dip, but the President's using the ocean."*

*Dr. Francis Leo Golden: Jest What the Doctor Ordered.

Chemotherapy for Genitourinary Malignancy

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STRATEGY FOR CANCER chemotherapy is applied through a knowledge of cell kinetics, drug activity and disposition, drug-host-tumor relationships in regard to host toxicity and anticancer effect; and combination of chemotherapy with surgery and/or radiation.

Cancer chemotherapy has been relatively more successful in those tumors which are more rapidly growing with a large proportion of cells in mitotic cycle. The cells in their proliferative state are sensitive to the cell-cycle-stage-specific drugs (antimetabolites). However, the normal, highly proliferative cells of the intestine and bone marrow are also prime targets, and damage to these essential tissues is a limiting factor in chemotherapy. Due to the rapid recovery proliferative regrowth of the intestinal epithelium, toxicity to the patient by sublethal doses is delayed or reduced.

Extent of Disease

Failure to respond to chemotherapy characteristically occurs in slow-growing human solid tumors which are usually found in the older age groups. These often remain localized at the primary site for long periods, growing slowly; but when spread does take place, growth is often rapid. These advanced and metastic cancers generally have a low thymidine index, low tumor doubling time and low growth fraction.

Whereas surgery and radiotherapy are limited in application for cure by the presence of anatomic dissemination (local spread and metastases), chemotherapy is based on the total number of tumor cells and their proliferative state. However, by the time a tumor is large enough to be clinically palpable, it is already too large for total eradication by chemotherapy. The best use of drugs with proper scheduling, routes of administration, and combination (alkylating agents as cell-cycle-nonspecific and antimetabolities as cell-cycle-specific) may give some degree of success when the cancer cells are killed faster than they can be replaced. The repetitive therapeutic courses could succeed in eliminating the viable cells or converting them to "sterile" cells if treatment could be repeated after host recovery but before tumor recrudescence. However, to date, destruction of all the malignant cells has not been possible since the drugs available are not sufficiently specific, have low therapeutic indices, and are limited by their host toxicity. Obviously, chemotherapy is most effective when treatment is given early to a small tumor.

Endocrinologic Approach

Since sex steroids can stimulate growth and cell division (increased fraction of cells proliferating), their combination with antimetabolites may increase the sensitivity of the tumor to the antimetabolite which is effective against the actively proliferating cells.

Androgen stimulates prostatic carcinoma in vivo and could simultaneously increase the antimetabolite sensitivity of the tumor, as compared to the bone marrow and intestinal epithelium. Simultaneous use of androgen and P32 in prostatic cancer has been previously reported, Thus, the combined use of androgen with some combination of Fluorouracil (5-fluorouracil or 5FU), Methotrexate (4-amino-N methylpteroylglumatic acid), and Cytoxan (cyclophosphamide) should be tried where the tumor has escaped estrogen and castration control.

Progestin added to other sex hormones may effect a greater carcinostatic response, such as giving Provera (medroxyprogesterone) with diethylstilbestrol in carcinoma of the prostate, presently undergoing clinical trial by the Veterans

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Administration Cooperative Urologic Research Group.

Therapeutic Combinations and Schedules

Combination therapy allows for administration of full doses of two or more drugs when their individual host toxicities (different mechanisms of action) vary. Sequential combination therapy first uses an alkylating agent (cell-cycle-non-specific) to kill as many tumor cells as possible, then follows with an antimetabolite (cell-cycle-specific) to attack the remaining cells which have become sensitive by starting to divide. Combination therapy may increase the speed of obtaining a remission; but in solid, slow-growing tumors, it may be difficult to demonstrate a difference between it and single drug therapy.

Early therapy and reduction of the tumor mass are important. Treatment is best given when there is the least tumor, obviously right after surgery, which has changed the tumor's biological status to that similar to a newly diagnosed tumor. The remaining cells may then be relatively more susceptible to chemotherapy. Surgery can be considered a remission-inducing agent since it can reduce tumor size over 90 per cent with minimal toxicity to the host.

Remission

Using chemotherapy, the chances for a complete cure are remote, but a temporary remission, even to five years without evidence of disease, is of therapeutic value.

Several factors may affect the induction of a remission. The relative toxicity of the drug(s) for the tumor cell and the host regulates the doses given, over what length of time, and how often repeated. The number of tumor cells, the development of resistant cells, and localization in remote body areas offer increased obstacles to tumor eradication.

Effective chemotherapy can be expressed as unmaintained remission after treatment or in terms of survival. Repetitive periodic courses of treatment for long-term maintenance hopefully prolong remission and comfortable survival. In advanced, disseminated cancer, radiation therapy is usually more detrimental than beneficial. At this point, combination chemotherapy may induce prolonged remissions. Six courses of drug therapy (five days or more) are given initially, each course followed by a rest period of two weeks.

Most tumors need multiple drug therapy, employing surgery and/or radiation with repetitive drug courses to induce remission, prolong remission by maintenance, or as prophylaxis to delay appearance of metastases and prolong survival. If drugs can cause regression of clinically detectable tumor, they should also affect microscopic foci. Thus prophylactic chemotherapy in the absence of grossly detectable disease should be profitable in preventing or delaying local recrudescence or distant metastases. Reserving chemotherapy until tumor recurrence becomes clinically evident is definitely not an answer to the problem of tumor cell elimination.

Toxicity

Host toxicity by chemotherapeutic agents relates mostly to the bone marrow and/or the gastrointestinal mucosa. These effects represent the limiting factor preventing the administration of sufficient drugs long enough to obtain total or almost total tumor cell kill. Usual complications include nausea, vomiting, stomatitis, diarrhea, constipation, hepatotoxicity, alopecia, peripheral neuropathy, leukopenia, anemia, and thrombocytopenia. Treatment of these complications generally requires reducing the dose or discontinuing the chemotherapy.

Thrombocytopenia seldom results in serious hemorrhage when platelet counts are above 20-50,000 per cmm; however, below this, platelet transfusions become necessary, either as fresh whole blood, platelet-rich plasma, or platelet concentrates.

Severe granulocytopenia may result in gram-negative septicemia, especially Pseudomonas, in spite of prophylactic antibiotics. Fatal sepsis is a major difficulty in modern cancer chemotherapy. Leucocyte transfusions are not common, as suitable donors or technology are not often available.

Patient isolation in a sterile environment while they are receiving intensive chemotherapy has been found workable, using either a bed enclosed in a large plastic canopy or a laminar air flow isolator which can be portable.

Immunotherapy

Practically all physical and chemical carcinogenic stimuli act to suppress immunologic response. Immune capability is lost as a cancer

grows, but in early, operable stages, no inhibition can be shown. Cancer tissue has antigenic properties absent in normal tissue. Tumor antigen can either stimulate the production of antibodies and specifically sensitized lymphoid cells or produce a specific paralysis of immunologic response, often depending on the age of the host.

In malignant tumor, there is progressive growth in the presence of immunity, and it seems that the failure of a host to reject his own tumor is due to the fact that he has become tolerant to its antigens. Transplantation immunity and tumor immunity have points of similarity. Laboratory and clinical information define active defense immunologic effects by the host against his cancer, but somehow they fail to eliminate the cancer cells.

Chemotherapeutic use and results must consider that any drug which causes bone marrow aplasia is also immunosuppressive and may result in reduced therapeutic effects by blocking the host's tumor response. Improved therapeutic effect would result from a synergism between the drug and the immune response of the host against the malignant tumor. If used sequentially, chemotherapy and immunologic stimulation would not conflict. Thus the outcome of chemotherapy can be altered either way by the response of the host's immunologic apparatus.

Some Clinical Applications of Chemotherapy

The minimum criteria for patient selection for chemotherapy, in general, would be good nutritional status with good bone marrow function, and an absence of impaired hepatic function (or extensive hepatic metastases), impaired renal function, existing infection, or previous extensive radiation or chemotherapy. At times, the weakened patients may be prepared for, or sustained during chemotherapy by intravenous or nasogastric tube hyperalimentation using appropriate high-protein and high-carbohydrate mixtures.

The correction or improvement of existing infection, secondary anemia, and malnutrition should be made prior to starting chemotherapy and continued as required during and between therapy courses. Surgical adjuvant chemotherapy has been advocated on the basis that it may kill cancer cells remaining after surgical and/or radiation treatment; destroy cells in areas outside of the surgical or radiation sites; inhibit metastatic implantation of circulating clonogenic cells; and prolong survival.

Prostate (including personal unpublished data)

The use of estrogen and/or orchiectomy has been very widely employed since Huggins and Hodges published their report in 1941. After varying periods of therapy (months to years), the prostatic malignancy may become estrogen-resistant, recrudescent, and widely disseminated. Alkylating agents, especially Cytoxan, will then give a subjective response in a fair proportion of patients. Cytoxan 50 mg. bid orally for varying periods, at least eight to 12 weeks, followed by return to estrogen therapy (carbestrol, or diethylstilbestrol) has, at times, resulted in a palliative objective and subjective remission from one to three years. Immediate relief with Cytoxan may not be evident, but enhanced or repeated response to the sequential estrogen has been quite gratifying in several patients.

Later, repeated courses of oral Cytoxan 50 mg. bid alone or with oral Methotrexate 2.5 mg. tid were given to toxicity while continuing daily oral estrogen (carbestrol 20 or 100 mg.) or diethylstilbestrol (1 to 5 mg.), during and after the chemotherapeutic courses.

Recently, an intravenous regimen for more intensive initial therapy of treatment failures has been employed, giving a daily mixture of Stilphostrol 1 gm. and Cytoxan 400-600 mg., with Methotrexate 2.5-5 mg. added three days a week. This is administered to toxicity and followed by daily oral estrogen (carbestrol 20 mg. or diethylstilbestrol 1 mg.) as maintenance. Consideration should be given to using this intravenous combination in courses of five days every several weeks, depending on response, or giving one treatment weekly or semi-monthly. As more clinical experience in the use of these combinations is accumulated, further modifications of schedules and/or drug combinations to enhance response will be undertaken.

Pelvic arterial infusion therapy should be tried if painful pelvic osseous metastases or local invasion of the urethral bulb or perirectal constriction are not otherwise controlled. Thought also should be given to simultaneous cobalt radiation limited to these isolated areas.

Kidney

1. Hypernephroma

Renal carcinoma may grow slowly and its metastases remain indolent, or very occasionally re-

gress spontaneously. Various treatment combinations have shown varying degrees of effective palliation, especially for recurrences or metastases. Hormonal therapy with Provera or testosterone appears promising. Varying combinations of Cytoxan and chlorambucil, with either fluorouracil (5FU) and/or actinomycin D have induced remissions in a limited number of patients. The addition of radiation and/or hormonal drugs to these drug schedules may enhance their effectiveness. Preoperative use of radiation with chemotherapy may convert a large hypernephroma to an operable lesion and, at the same time, decrease the size of the dilated venous supply, facilitating surgical excision. Daily oral Cytoxan with periodic intravenous courses of Cytoxan (daily for five to 10 days, or to toxicity) has been employed as maintenance therapy, especially in metastatic and recurrent lesions.

2. Wilms's Tumor

In this category, the largest number of long-term survivors have been those treated with the combination of surgery, radiation and actinomycin D. This antibiotic seems to potentiate the postoperative radiation and is administered beginning the day of surgery. Bi-monthly five-day courses are given to delay the development of metastases or prolong survival when metastases occur. Vincristine may be used instead of the actinomycin D, or in combination with it, especially because of the lack of bone marrow toxicity by the vincristine. Increased effective response has been reported using the triple combination of actinomycin D, vincristine and Cytoxan.

Testicle

Over-all, in testicular tumors, actinomycin D with an alkylating agent (chloroambucil, Cytoxan or sarcolysin) and an antimetabolite (Methotrexate) has been used in double and triple combinations. In some therapy regimens, quadruple therapy has been given, adding vincristine and also alternating the use of mithramycin and the actinomycin D in successive courses.

Therapy must be individualized depending on the resulting toxicity. Objective remissions, as well as subjective improvement, have been reported in a fair proportion of patients with metastatic testicular carcinoma. Therapy should be continued at regular intervals during a remission for at least two years, and probably three, in an attempt to maintain this regressive status. Chemotherapy should be started at the time of orchiectomy and lymphadenectomy for the best chance to obtain a better and prolonged survival.

All patients with advanced and disseminated testicular cancer, who are capable of tolerating the ensuing toxicity, should be treated with multiple drug chemotherapy. Response can be gauged by determining the progressive levels of urinary chorionic gonadotropin and/or size of the pulmonary metastases.

Bladder

Chemotherapeutic agents are applied by topical, oral and intravascular (intravenous or intra-arterial) routes in combination, and/or with surgery and/or radiation in carcinoma of the bladder. Intracavitary use of thio-TEPA (n, n', n"-triethylenethiophosphoramide) has been favorably reported in treating multiple papillary tumors, and for palliation in hematuria of advanced invasive cancer where cystectomy was not feasible. Direct intra-tumor endoscopic injection of thio-TEPA for palliation has been of value.

Intravenous anticancer drugs should be given in combination (1) with other oral or intravascular anticancer drugs, simultaneously or sequentially and (2) with surgery and/or radiation therapy. The chemotherapy may be given preoperatively, concomitantly with radiation or in postoperative or post-radiation scheduled periodic courses. The value of fluorouracil alone has been seriously questioned by Prout and associates, but others have obtained effective response with the combined use of fluorouracil with surgery and/or radiation. However, the trial of combined cell-cycle-stage-non-specific drugs (such as Cytoxan) with periodic courses of concomitant or sequential cell-cycle-specific drugs (such as Methotrexate, flourouracil, 6-mercaptopurine, actinomycin D, vincristine, etc.) may at least give palliative relief and possibly increased survival.

The intra-arterial route has been employed best by prolonged, slow, continuous arterial infusion for weeks or even months. The pelvic arterial perfusion method is more complex. The main use has been for palliation (relief of pain and/or hematuria) in symptomatic far-advanced bladder cancer, mainly using Methotrexate. The combined and/or sequential periodic use of Methotrexate with cell-cycle-stage-non-specific drugs (mainly alkylating agents, such as Cytoxan, thio-TEPA, nitroso-urea, etc.) and cell-cycle-stage-specific

agents (fluorouracil, etc.) should be considered for possible greater carcinocidal result.

Prolonged pelvic infusion is given via the hypogastric arteries by open pelvic surgical placement of the catheters, or by catheterization of the inferior gluteal or inferior epigastric arteries. Cutaneous transfemoral placement of a catheter into each iliac artery or one catheter above the bifurcation of the abdominal aorta may be used.

Complications do cause one to weigh the benefits to be derived against the morbidity of the procedure. Drug toxicity, sepsis and technical catheter and vascular replacement failures (hemorrhage of artery perforation, thrombosis of artery or catheter, leakage outside catheter, and displacement of catheter) may occur with intra-arterial chemotherapy. In addition, this procedure should be done by an experienced chemotherapist in a center with all the necessary technical equipment and supporting auxiliary personnel for careful nursing care and supervision. It has been suggested that the patients who do give a significant response to this procedure might have responded equally well to systemic chemotherapy and/or radiation.

Summary

Cancer in some form presents itself to practically all physicians for diagnosis and therapy. The general practitioner and the specialist in any anatomical area are faced with management of cancer in all stages. The urologist has his full share of therapeutic problems in urogenital cancer.

The challenge of using chemotherapy is open to the physician who cares enough for the patient to invest the increased effort and time to learn the principles of chemotherapy. The frequent therapeutic failures resulting demand a greater and renewed dedication by the physician, but experience and knowledge are gained both in the art of chemotherapy and the understanding of cancer by treating each patient, no matter how confusing, complex and hopeless his problems and status may be. There must never be a lack of treatment, as this conveys to the patient the fear that his situation is hopeless.

Cancer chemotherapy reassures the patient that he is being actively treated for his cancer. The frequent laboratory tests, progress roentgenograms, and daily physician contacts to evaluate the patient and his tumor response to the cancer drug, all give the patient reassurance that he has not been abandoned as hopeless. In the very ill patient, chemotherapeutic agents are available that will not add to his distress. Throughout, the physician must hold a hopeful and optimistic attitude. For the patient to better cope with the discomfort of chemotherapy and its side-effects, the physician must keep his patient reasonably informed.

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Train your child in the way you now know you should have gone yourself.
—Charles Spurgeon

A Letter To A Friend

Dear Jack (John Oliver LaGorce): June 22nd, 1944

In reply to your request for information, my local doctor asked me to go to Boston to see Dr. Samuel Levine, the distinguished heart specialist, so that he could find out how much snake oil he dared to shoot into me for my polyneuritic hands. The great heart specialist found nothing wrong with my heart, but decided to take over my hand situation himself and consequently ordered me into the Peter Bent Brigham Hospital for eight or nine days so that a series of tests could be made of my droppings, skin scrapings, hair follicles and other excretions. I may say that Levine and his colleagues at the Peter Bent Brigham gave me one of the most thorough overhaulings ever experienced by anybody except a murder suspect. They prodded and thumped me and probed me with blunt instruments and even with their fingers. They peered down my throat with electric lights and peered up my tail with periscopes. They electrocardiogramed me and glucosed me and thiamined me and gave me stuff to bring out all the rainbow tints of my gall bladder; and when they had shaken me up to such an extent that they had my greater intestine knotted around my tonsils, they gave me chloral hydrate to calm me down until they could get their tools sterilized for the next day's session.

As a result of all this probing and prying, they found that my heart, lungs, liver, gall bladder, eyes, teeth, nerves, reflexes, kidneys and other internal odds and ends were completely undiseased and normal. This, they argued, couldn't possibly be true, on account everybody has got to have something the matter with him besides just a couple of sore hands; so they went over the whole thing again.

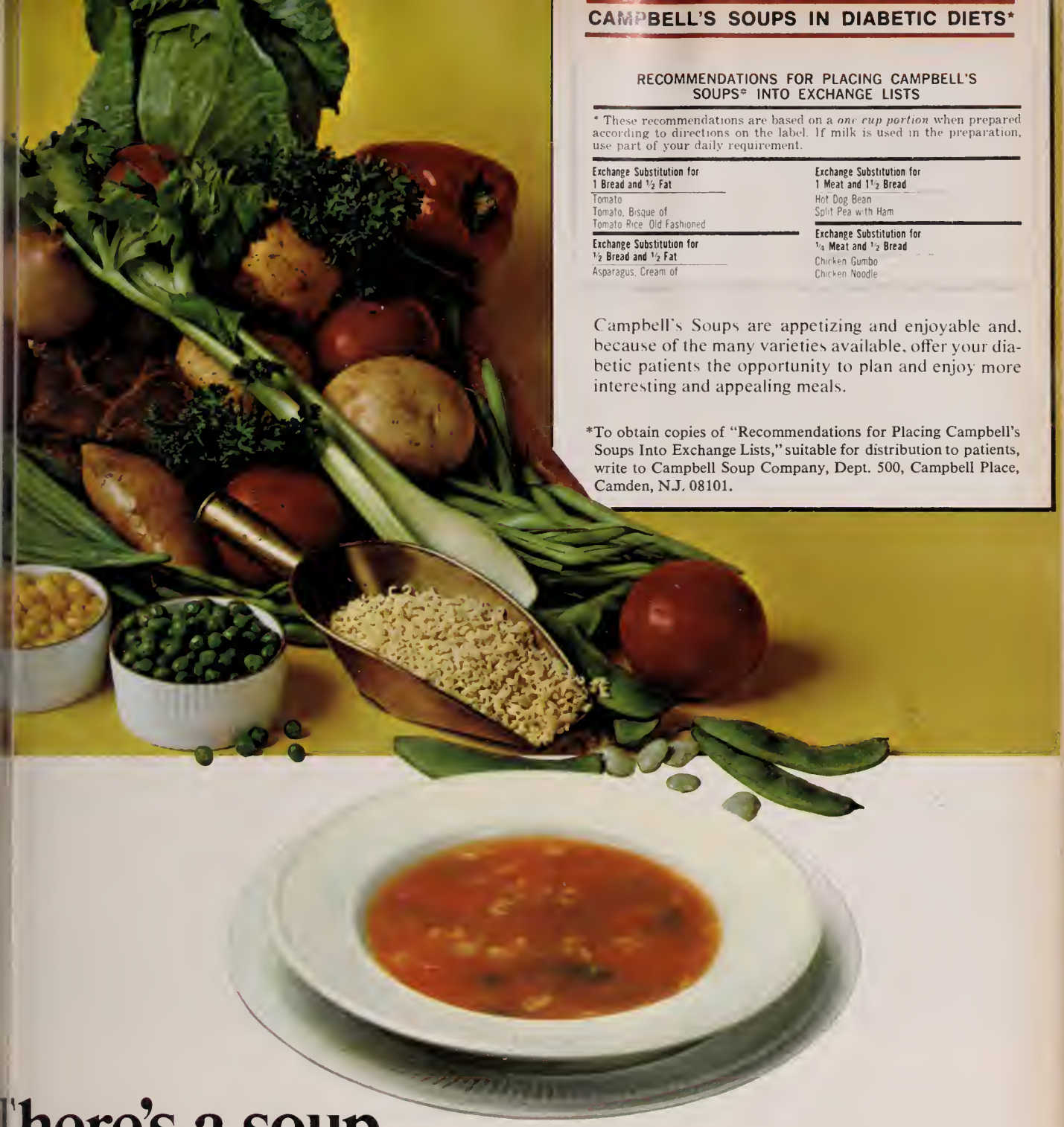
From the arguments of all these eminent fellers I gathered as follows: It was absolutely certain that I didn't have polyneuritis. One doctor felt sure I had incipient gout, but it was so incipient that it hadn't yet shown up, so that he couldn't prove it. Another was strongly of the opinion that although the x-rays showed nothing wrong with my neck or spine, he believed that there was an arthritic condition somewhere around there that had a reflex spastic influence on my hands.

The distinguished diagnostician, Dr. Robert Monroe, said pleasantly that all these opinions, according to his way of thinking, were so much horse crap: he had studied all the x-rays and scrapings and droppings, and had even gone so far as to smell and taste them, and he felt perfectly free to state that they showed conclusively that I had no polyneuritis, no gout, no arthritis and no rheumatism. My trouble, said he, was that I had rested all my girlish weight on my left elbow for too many years while writing 800-page books, and that this posture had resulted in a periarticular fibrositis (a pain in the hands to you), and that this unfortunate condition, in his opinion, could be rectified if I fell flat on my back for half an hour three times a day and would stop using a pillow when sleeping.

Accompanying all these opinions were a lot of suggestions as to eating and drinking, each doctor holding out for me to eat what he likes to eat, and to go without the things of which he disapproves. Thus some of the doctors thought I should go without liquor; others thought I could take several cocktails each night without any deleterious effects. Doctor Levine, who had first refused to countenance the use of any liquor at all, gave it as his opinion that one highball a day was permissible: still others thought I would do well to go without liquor six days a week and tank up freely on the seventh.

I trust this tells you what you want to know about my physical state. If it does, please let me know what's wrong with me, because I'm not at all sure myself.

*Written by Kenneth Roberts (1885-1957) and quoted in A Mirror up to Medicine by A. C. Corcoran, M.D., 1961. (K. R. was an American novelist.)



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An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication—Ovulen and Demulen are indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality conducted in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Ovulen and Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Ovulen or Demulen. Therefore, if such tests are abnormal in a patient taking Ovulen or Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen or Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen or Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen or Demulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen or Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values, metyrapone test and pregnanediol determination.

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Editorials

Surgical Management of Peptic Ulcer

Approximately 10% of patients with peptic ulcer require surgery and, despite the development of potent anticholinergic agents, antacids, good psychiatric therapy, and improved dietary control, this figure, in the last three decades, has not been reduced. In fact, with an increase in the number of patients developing the disease, the total number requiring operative management has increased proportionately. Since in excess of 20 million people in the United States suffer from the various manifestations of peptic ulcer diathesis, the problem is of considerable socioeconomic as well as medical importance. In short, peptic ulcer is a major public health problem. However, controversy directed at "ideal" operative management of peptic ulcer continues. A substantial amount of clinical and experimental research has been directed at some of the subtler pathophysiologic aspects of the disease, and clues leading to a satisfactory approach appear to be emerging.

Although the lesion may occur at any level of the gastrointestinal tract from the esophagus to the colon, it is, of course, most common in the stomach and duodenum. That gastric and duodenal ulcers, however, are different clinical entities can be properly inferred from the sharply different social and epidemiologic patterns of the two diseases. The vocational and educational backgrounds and familial distribution, age, blood groups, and sex, all differ in gastric and duodenal ulcer. The usual patient with gastric ulcer is more likely to be female, is on the average a decade older, and tends to come from a lower socioeconomic status level than the usual duodenal ulcer patient. Moreover, and probably of greater significance in terms of treating the patient, studies of gastric acid secretory output and motor patterns lead one to the almost inescapable conclusion that the two types of ulcer, although apparently similar, differ in many fundamental ways. Duodenal ulcer patients consistently make too much or normal amounts of acid, while gastric ulcer patients secrete normal or less than normal amounts. Lastly, and most importantly from the point of view of the practicing physician, evidence is accumulating to suggest that the two entities respond *very* differently to surgical therapy.

Most surgeons have evolved an operative approach to the treatment of peptic ulcer and have become comfortable in their particular choice of procedure. Whatever the individual variation and preference in surgical management of duodenal ulcer, some facts have emerged. It would appear from the mass of data accumulated both in the United States and in England, and supported as well by statistics gathered from many European clinics, Australia, and South Africa, that the safest operation, from the point of view of overall mortality, is vagotomy and a drainage procedure. It is, moreover, very well tolerated in terms of morbid complications and suffers only from a relatively high (5 to 9%) recurrence rate. The most effective operation in terms of low recurrence rate appears to be vagotomy and antrectomy or hemigastrectomy. The virtually 0% recidivism after this procedure is marred, however, by the relatively high (2 to 4%) mortality rate. Finally, advocates of subtotal gastrectomy—a long-respected and well-established procedure—seem to be on the wane, since this procedure is neither the safest nor the most effective of the three.

The two operations utilizing vagotomy as their cornerstone appear to have gained a substantial following and are, apparently, here to stay. In many clinics vagotomy and a drainage procedure are the standard operative approach to the garden-variety duodenal ulcer. In patients who are alcoholic, or who have a particularly virulent jejunal ulcer, or who are required to take drug therapy which may be of an ulcerogenic nature (i.e., aspirin or steroids for arthritis), the treatment of choice is felt to be vagotomy and antrectomy. Utilization of these approaches appears to make most effective use of the respective recurrence and mortality rates for each of the operations.

It can generally be stated that the characteristic morbidity, mortality, and/or freedom from side effects after various types of surgery are less clearly defined for gastric than for duodenal ulcer —although they are by no means clarified for either. For gastric ulcer, the data supporting one or another of the standard operations are not nearly so persuasive. Although in some series utilizing vagotomy and drainage for benign gastric ulcer* results are spectacular with 0% recurrence and mortality, others† have reported a much poorer response (35% ulcer recurrence rate). There are, moreover, a number of good series almost uniformly supporting the concept that gastric resection (subtotal gastrectomy) for gastric ulcer carries a low morbidity and recurrence rate; the data for vagotomy and drainage for gastric ulcer are far less consistent. There is growing, strong supportive evidence for the concept that the proper surgical treatment of gastric ulcer requires that the ulcer and the antrum be removed.

The problem of surgical management of gastric ulcer is further compounded by the fact that upwards of 20% of these patients have a coexistent duodenal ulcer. Under these circumstances the characteristic secretory and motor patterns, age, and other epidemiologic factors tend to be those of patients with the duodenal lesion rather than the gastric ulcer. It would seem, therefore—and current data bear this out—that these patients should be treated primarily as virulent duodenal ulcer patients probably best handled by vagotomy and antrectomy.

It is apparent then that gastric and duodenal ulcers are basically different diseases. They are different because the age and sex of the patients are different, the size of the parietal cell mass is different, the motor and secretory patterns are different, the characteristic blood groups are different, and, most importantly, these diseases are different because they respond differently to different forms of surgical therapy.

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*Farris and Smith: On Current Surgical Management, Vol. 3, S. B. Saunders & Co., Phil., 1965.
†Stemmer, E. A., et al: Arch Surgery 96: 586, 1968.
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A Medical Perspective of Surgery for Coronary Artery Disease

REVASCULARIZATION SURGERY for coronary artery disease, especially the reversed saphenous vein technique, can produce relief of severe and incapaciting angina pectoris. The recent report of Garamella et al.* provides an excellent perspective of the surgical approach to this disease, with major emphasis on anatomic considerations and early mortality.[1] From the perspective of internist and cardiologist, however, it raises more questions than the behavior of the grafts and their effect on patient survival.

The concept of applying high-risk surgery to disease primarily because it is arteriographically demonstrable, while giving secondary consideration to the extent of symptoms and the risk of conservative treatment, would seem to deserve clarification and comment. While the theoretical ideal of immediate augmentation of coronary blood flow may need "no defense in concept," its application deserves consideration of relative risks and the chance of success in relieving symptoms. The report of Garamella gives neither the breakdown of patients in the categories listed as indications for surgery, nor the percentage of patients who showed improvement, whether symptomatic, physiologic, or electrocardiographic. The assumption appears to be that alteration of anat-

*Minnesota Medicine, December, 1970, page 1227.

omy and coronary blood flow will ultimately affect mortality and morbidity regardless of the symptomatic state of the patient before or immediately after surgery.

The implications in the Garamella report prompt a brief and preliminary description of experience with 425 consecutive patients of all ages seen over approximately a two-year period for known or suspected chronic coronary artery disease. Although these represent only a fraction of such patients seen during this time at the St. Louis Park Medical Center and since long-term follow-up is not complete enough to permit dogmatism, the statistics are representative of a different perspective and approach to the problem.

Patients in this series were not considered candidates for surgery unless they were severely symptomatic from angina pectoris that was unresponsive to medical therapy (control of weight and blood pressure, and high-dose propanolol therapy.) Arteriography, ventriculography, and ventricular pressure studies were used in 54 patients for diagnostic accuracy, to provide anatomic and physiologic correlation with symptoms and to determine the feasibility of surgery and the best technique.[2] Average follow-up has been 12 months (3-27 months).

The 425 patients can be conveniently divided into four groups according to symptoms and diagnosis. The first 175 patients consisted of those in whom coronary disease was suspected but could not be established by conventional diagnostic methods. The second group of 128 patients consisted of those who had had a documented previous myocardial infarction but who were subsequently asymptomatic (class I), and patients who had angina predominantly with strenuous exertion (class II). The third group consisted of 66 patients who had frequent or severe angina occurring predominantly with usual non-strenuous daily activities (class III), and patients with spontaneous angina or episodes of prolonged coronary insufficiency occurring at rest or in bed (class IV). The fourth group consisted of 61 patients who had cardiomegaly or heart failure due either to known or to suspected coronary artery disease.

Sixteen patients underwent surgical procedures. Eleven had attempted vascularizations with one surgical death, two carotid sinus stimulators (Angistat, Medtronics)[3], one aneurysmectomy, and one valve replacement or papillary muscle dysfunction; one patient had an attempted revascularization procedure elsewhere for heart failure without angina but died the date of surgery. All of the patients who underwent surgery were under 70 years of age and had surgery for either class III or class IV angina or for left ventricular failure.

In the remaining 234 patients with documented heart disease who did not have surgery there were 26 deaths (mortality rate 11 percent). However, 20 of the 26 deaths occurred either in those patients over 70 years of age or in those with cardiomegaly and heart failure, a group in which surgeons are not anxious to attempt revascularization procedures. In a group of 97 patients under the age of 70 who were asymptomatic or had class II angina there were two deaths (2 percent). In a group of 42 patients under the age of 70 with class III and IV angina there were four deaths (9 percent mortality).

Certain implications seem apparent from these statistics. It appears unlikely, or at least unproven, that applications of surgery with an approximate 10 percent early mortality will decrease the total mortality in patients with atypical or minimal symptoms (groups 1 and 2). Only in groups 3 and 4 does the total mortality (early and late, to use surgical terms) of medical treatment approach that of the 30-day mortality of surgery. It is possible that the survivors of surgery may have an ultimately better prognosis if their functional classification is improved as a result of the surgery. Surgery, therefore, seems justifiable if the patient is severely symptomatic and has a good chance of having both symptomatic relief and a better prognosis as a result of surgery. This is consistent with the usual principles applied to surgery for valvular heart disease.

Of the 10 patients who survived revascularization surgery (five Vineberg, five reversed saphenous vein grafts) all but one seemed to be symptomatically improved, some dramatically so. Some patients with abnormal preoperative treadmill exercise electrocardiograms were negative postoperatively. One patient, however, deteriorated again to severe class IV angina 10 months after surgery and the revascularization vessel was demonstrated to be closed by arteriography. Three of four patients who had carotid sinus stimulator insertions at the St. Louis Park Medical Center (two in the above series) are still alive and three have much better control of their angina. These

patients had severe diffuse distal coronary disease not considered ideal for surgery; one had severe hypertension and two, diabetes mellitus.

The adjective "disabling" may justify surgery for angina pectoris in an individual patient but is of little value in determining the effect of surgery on the natural history of the disease in that individual or in larger populations. A manual laborer may be "disabled" by class II angina but an office worker or retired person may continue to function quite well with medical control of class III angina. It is a rare person who would want to take advantage of surgery, if he wishes to be less active, to be asymptomatic on the golf course, considering the 10 percent immediate risk of surgery to the one year, 5 percent risk without it. Furthermore, increasing numbers of verbal reports of a 20 percent closure of grafts at one year would make most prudent physicians and patients consider waiting until either the symptoms are worse or the long-term results are better defined before strongly considering surgery.*

At the present time the opinion of Dr. Berman† questioning the application of high-risk surgery to minimally symptomatic patients with coronary artery disease seems justifiable, and the approach of reserving surgery for severely symptomatic patients seems more reasonable. Until those who are extensively applying surgery to patients with coronary disease prospectively (not restrospectively) classify patients according to symptomatic groups for comparison with the natural history, reports of surgical experience will be of little help in proving the superiority of surgical treatment in the minimally symptomatic patient.

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*Reports at 1970 Minneapolis Methodist Hospital Symposium, and American College of Cardiology Symposium "Advances in Heart Disease", San Francisco, December, 1970.

†Cardiology Section, St. Louis Park Medical Center.

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Hepatorenal Toxicity of Tetracycline

I WELCOME THE opportunity to comment on the paper of Breitenbucher and Crowley that appeared in the September issue* on the general subject of tetracycline therapy in high-risk patients. The authors have performed a great service by calling attention to the catastrophic results that may occur with overzealous use of intravenous tetracycline. This situation is most clearly documented in pregnant patients given doses generally in excess of the recommended 1-2 grams per day. The syndrome of hepatotoxicity and negative nitrogen balance probably occurs more frequently than we suspect in patients with borderline renal failure given ordinary therapeutic doses.

To my knowledge, direct renal toxicity of undegraded tetracycline has not been clearly demonstrated in man or animals. Not only is blood urea nitrogen a fickle measure of renal function (highly dependent on nitrogen balance and rate of urine flow), but severe hepatic disease by itself is well known to predispose to renal failure.

A further troublesome feature concerns the continuing problem of cause and effect relationships. All of the seven patients presented in the current report suffered from life-threatening disease. Almost all had had recent major surgery, were elderly, and had renal disease. How can one really dissect these particular cases out from the bulk of similar patients who die without the "benefit" of tetracycline? Fine fatty infiltration of the liver is, to my nonpathologic eye, a nonspecific finding and hardly characteristic of tetracycline toxicity alone. The renal findings are also nonspecific. Double blind studies of liver sections from patients dying of a variety of causes while receiving different drugs are essential before attempting a diagnosis of tetracycline hepatotoxicity based on morphologic data. Tetracycline is highly concentrated in the liver. This might permit tissue levels at post mortem to be a useful guide in

*Breitenbucher, R. B. and Crowley, L.V.: Hepatorenal Toxicity of Tetracycline. Minnesota Med 53:949, 1970.

examining specimens in future studies. It would seem reasonable to try to relate tetracycline content to fatty infiltration at autopsy.

Despite the difficulty in implicating tetracycline as a toxic agent in individual cases, caution must be used to avoid potential problems. The drug is removed from the body primarily by the kidney. Patients with renal failure will retain the drug, and high concentrations in the blood are to be expected if ordinary therapeutic doses are continued. Good examples of high levels are given in the report in this issue. Dose schedules can be constructed to avoid this; a loading dose in adults of 500 mg. should produce adequate therapeutic levels. The half-life of tetracycline in serum is about eight hours. In patients with normal renal function repeat doses two to four times a day will maintain good levels, depending on the dose used. In anuric patients the half-life of tetracycline may be as long as 110 hours. Repeat doses at three-to-four-day intervals should be adequate for severely uremic patients, yet not excessive. Patients with moderate renal insufficiency (creatinine clearance between 10 and 30 ml. per minute) should receive doses repeated at one-to-two-day intervals to avoid accumulation.

It is hoped that choice of the proper indication for tetracycline plus modified dose schedules will avoid the potential problem of the tetracycline overdosage syndrome.

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Diplomacy

Marcus Aurelius had a sudden attack of intestinal colic at night and in spite of taking a dose of *hiera picra* and another of *Theriac,* he developed a fever. His physicians who attended him in the army ordered him to rest and eat nothing for nine hours except a little broth. These same physicians came to the Emperor's home where I saw them taking his pulse. I judged that he was becoming feverish but I said not a word, and when my turn came I did not even feel his pulse. This caused the Emperor to ask me, on the side, why I did not approach him, to which I replied that the others were better judges of the pulse than myself. But the Emperor held out his arm to me and I felt his pulse most carefully. I said that it indicated the beginning of a febrile attack caused by the undigested food which filled his stomach. My words so pleased Marcus Aurelius that he shouted, "That's it, you have put your finger on it exactly, I feel full." He repeated these same words three times. He then asked me how to relieve himself. "If it were anyone else," I replied, "than the Emperor, I should give him a little pepper and wine, as I have often done in similar cases; but since I have not been accustomed to administer such strong remedies to Kings, I would suggest the application to the abdomen of a woolen compress soaked in very warm oil of spikenard." Marcus Aurelius would have neither of these remedies but said to Pitholaus, "He is not only a physician but the only honest man around here."*

*Galen as quoted by Louis Lasagna in The Doctors' Dilemmas.

Editor's Note: Hiera picra—a cathartic powder made of aloes and canella bark. Theriac—a mixture of about 70 drugs pulverized and reduced with honey to an electuary.

Derivatively Speaking

Hormone—from Greek *hormaein:* to excite.



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Editor's Soliloquy

That Infamous City of Elsewhere

Even in my student "salad days" I used to hear the term "elsewhere" used to denote some other, often distant place, whence a patient had come and where he had undergone, in my naïveté, a "questionable" procedure or operation, after which the ensuing morbidity and sequelae became so portentous as to make it mandatory for him to be referred to our own esteemed institution where more accurate diagnoses and "definitive" care could be provided.

The arriving patient's history, taken by an ingenuous clerk or a conscientious first-year intern, generally noted the officially incorporated name of the city whence the patient had come, as well as the respected title of the local attending physician. However, by the time the more sophistical* Senior Resident or Junior Staff Man got around to inscribing his brief, captious notation, the patient's previous point of departure along with his doctor had both been compounded into "elsewhere;" a convenient capsule which gradually accreted a disparaging connotation, since treatment there had failed so dismally and dramatically as to necessitate the patient's referral.

In my unaffected simplicity I couldn't escape the conclusion that due to appalling and unpardonable professional incompetence or negligence the pitiful, if not desperate, patient had mysteriously and ignominiously contracted some unthinkable disease he would surely have been spared had he not happened into that den of iniquitous physicians stigmatized as "elsewhere."

In its laconic style the history would record that the patient had undergone such-and-such a procedure "elsewhere" and was now "presenting" here with this-or-that horrendous complication. For example: "A total abdominal hysterectomy and right oophorectomy was performed elsewhere five years ago and the patient now has inoperable carcinoma, probably originating from the left ovary."

In my mind "elsewhere" reduced itself to a pejorative, insinuating that "the infamous city of elsewhere" is the place where mistakes are made that have to be corrected "here." In its sly innuendo it hints at the below-the-belt punch, so inconsonant with professional dignity and honor!

Let's try to be more specific whenever possible by reducing "elsewhere" to its twin components of Dr. So-and-so in Such-and-such a City. Let's not forget that some—in fact, most—of our highly skilled and eminent colleagues practice "elsewhere," and, finally, that to *them* we too might have the occasion to be from "elsewhere."

Carl O. Rice, M.D.

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*Sophistical—intent to mislead or deceive by indifference to the correctness of one's reasoning.

OLD DOC HESS SAYS: Whether people dwell in homes made of brick, stone, stucco, or wood, they nevertheless all live in glass houses.

In Appreciation

Our Minnesota State Medical Association tradition for outstanding scientific sessions was unquestionably maintained during our 1971 Annual Meeting. In reviewing this meeting, we wish to acknowledge the significant contribution of our technical exhibitors. The overall quality of this meeting was enhanced by these attractive and informative exhibits. We express our sincere gratitude to the participating firms listed below and the hope that all will join our exhibition at each subsequent annual meeting. We sincerely urge that all of our Minnesota State Medical Association members join us in expressing our personal appreciation to these firms and their representatives.

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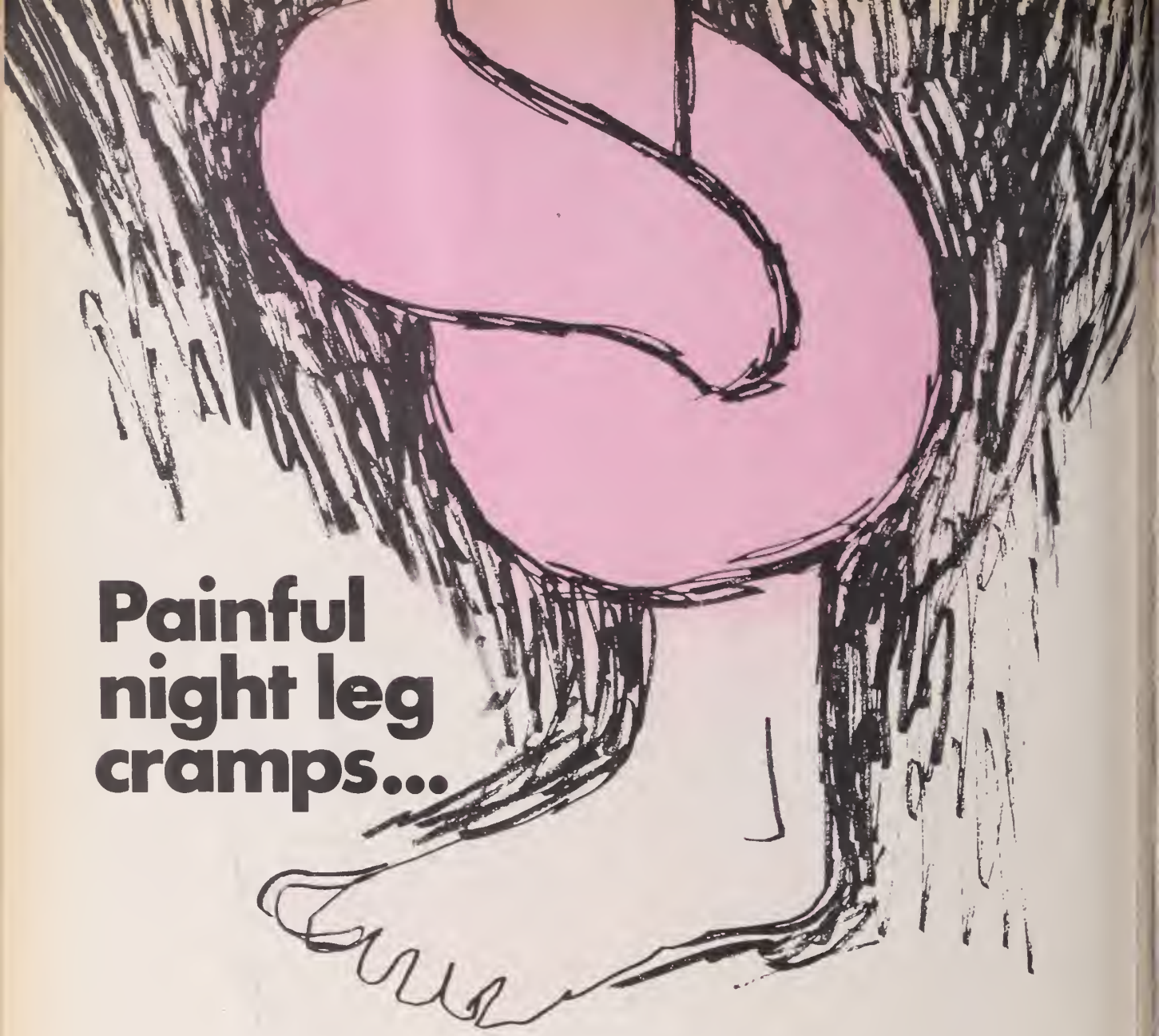
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The Viewing Box

Hematuria

With Dysuria and Urinary Frequency

THE PATIENT is a 74-year-old white male with a three-year history of hematuria, increased urinary frequency, decrease in urinary stream, dribbling, and dysuria. His hemoglobin was 11.0 gm percent. He had a normal white cell count with normal differential. The prothrombin time was normal. Blood urea nitrogen was 16 mg percent, serum acid phosphatase 1.6 King-Armstrong units with the prostatic fraction of 0.2 units. The urine was slightly turbulent with a specific gravity of 1.020 and was one plus positive for albumin and negative for sugar. The sediment revealed numerous white and red blood cells. The excretory urogram was unremarkable. At rectal examination a moderately enlarged prostate gland was felt. The lymphographic views are presented below. What is your diagnosis? (See next page.)



Figure 1

Diagnosis: Roentgeno and Lymphographic Analysis

Multiple increased densities are seen over the right ilium, both sacro-iliac joints and to a lesser degree in the left ilium and ischium. They represent multiple osteoblastic metastases typical of adenocarcinoma of the prostate. Figures 1 and 2 show the lymphangiographic phase of bilateral pedal lymphography and Figure 3, the 24-hour follow-up lymphadenographic phase. On Figure 1, one notices the large, centrally located filling defect in the inguinal nodes, but the flow through these filling defects appears unhampered as they represent benign fibrolipomatotic replacement of the lymphoid tissue. In the right external iliac node, one also notices a large filling defect; however, this is located in the peripheral portion of the node (arrow). Figure 2 shows the same lymphangiogram in a right anterior oblique view revealing, at the same right external iliac level, multiple abnormal lymphatic vessels (arrows). This almost reticular network is due to carcinomatous involvement, an impression further supported by findings on the lymphadenographic follow-up view (Figure 3). When comparing the right lymphatic system with the left, one notices the paucity of lymph nodes at the common iliac level at right. Contrast material (Ethiodol) is still seen in these abnormal appearing lymphatics. The large irregular cortical filling defect in the right external iliac node indicates replacement of lymphatic tissue by metastases (arrow). Although the osteoblastic metastases indicate prostatic carcinoma, involvement of the lymph nodes is more often seen in advanced carcinoma of the bladder.

Clinical Course And Discussion

This patient indeed had two primary malignancies. Adenocarcinoma of the prostate (Stage IV) had been diagnosed previously at transurethral resection, and the patient was placed on a comparative therapeutic prostate carcinoma trial study. Cystoscopic examination, repeated six months later, revealed another primary tumor in the bladder wall. Histologically it was a grade III transitional cell carcinoma with invasion of the muscular coat and perineural spaces. The patient was referred to radiotherapy. The lymphogram was very useful in mapping correct treatment



Figure 2



Figure 3

portals for the Cobalt 60 beam. All desired lymph nodes could be included in the treatment fields together with the primary tumors while at the same time unnecessary radiation to the normal structures was minimized. Both transitional cell carcinoma of the bladder and adenocarcinoma of the prostate can be considered moderately responsive to ionizing radiation. Favorable local response can be hoped for even in advanced cases.

Hans Kuisk, M.D., D.Sc.*
Minneapolis, Minnesota

*Chief, Radiation Therapy, Veterans Administration Hospital, Minneapolis, and Assistant Professor, Radiology, University of Minnesota.

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Cover Photo

Tropical Paradise

The 35 mm slide of the cover photo was taken by Dr. Bruce Linderholm while serving on the Medical Staff with the Project HOPE in Ceylon in December, 1968. This is the Indian Ocean on the Southwest side of the Island of Ceylon.

Dr. Linderholm is a urologist on the staff of Hennepin County General Hospital in Minneapolis and a Clinical Assistant Professor in the Department of Urology at the University of Minnesota. He is also in private practice in Minneapolis.

Table Tennis

The patient told her doctor she was so worried that she had butterflies in her stomach.

"Take an aspirin," advised the doctor, "and the butterflies will go away."

Whereupon the lady moaned, "But I took an aspirin—they're playing ping-pong with it now!"*

*Wisconsin Telephone News.





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Case Report

Spontaneous Conversion of Chronic Atrial Fibrillation of Twenty-two Years' Duration to Sinus Rhythm

RUSSELL HANSON, M.D.* and NAIP TUNA, M.D.†

ATRAIL FIBRILLATION is a common arrhythmia. When it develops, it can be either intermittent or chronic. There are numerous causes, the most common being arteriosclerotic heart disease, rheumatic heart disease, and thyrotoxicosis. Its reversion to sinus rhythm is well known with the use of drugs and electric cardioversion; however, spontaneous conversion of chronic atrial fibrillation to sinus rhythm is a rare occurrence. This report concerns a patient with atrial fibrillation of 22 years' duration who converted spontaneously to sinus rhythm.

Case Report

A 53-year-old married housewife who had had acute rheumatic fever at the ages of nine, 12, and 18 had developed ankle edema and shortness of breath during each of her three pregnancies, the last of which was at 18 years of age.

She was seen for the first time at the University of Minnesota Hospitals in 1938 at the age of 23, complaining of abdominal pain which was thought to be due to old pelvic inflammatory disease. A systolic murmur at the apex of the heart was heard. She was in normal sinus rhythm. She then returned to the University Hospitals in 1946 at the age of 31 for cardiac evaluation. She was found to have a holosystolic murmur at the apex of the heart associated with a mid-diastolic rumble and atrial fibrillation (Figure 1). Digitalis and a low sodium diet were prescribed.

She returned in 1954 complaining of increasing shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea. She underwent a left atriotomy with preoperative diagnosis of mitral valve disease, principally stenosis, but was found to have predominantly mitral insufficiency. The mitral valve was not repaired.

She was seen intermittently in the Cardiac Clinic with the same symptoms continuing. Serial electrocardiograms done in 1946 and 1947, April and May 1954, showed atrial fibrillation and right axis deviation.

In September 1962 a #2 Starr-Edwards prosthetic mitral valve was implanted. Cardiac rhythm continued

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†Associate Professor, Department of Medicine, University of Minnesota Hospital.
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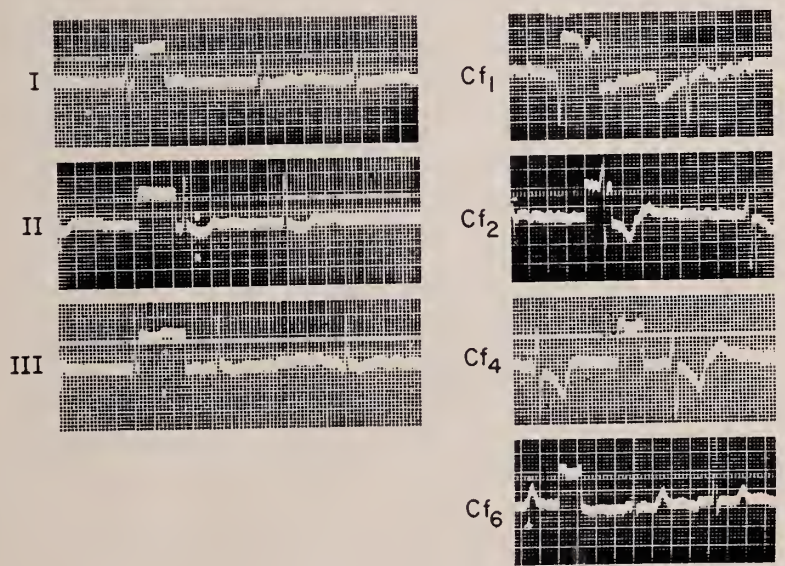


Fig. 1—July 26, 1946; atrial fibrillation.

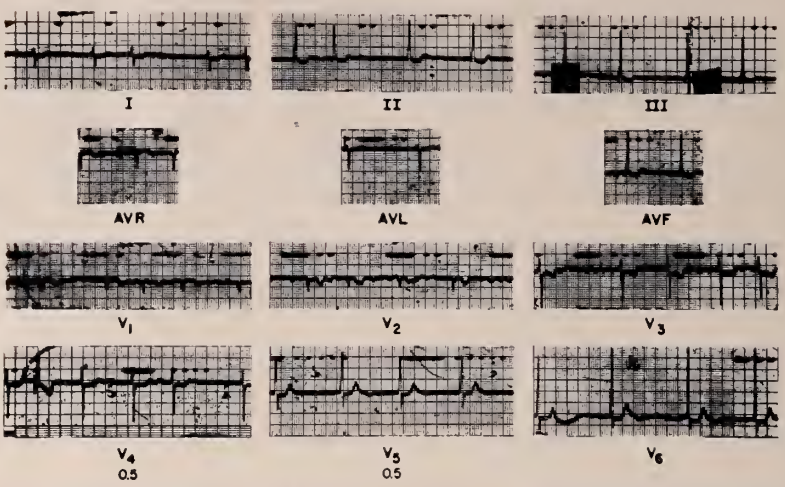


Fig. 2—September 4, 1962; atrial fibrillation, right axis deviation, biventricular hypertrophy, digitalis effect.

to be atrial fibrillation (Figure 2). Postoperatively her symptoms improved significantly. In February 1964 cardiac catheterization was performed and she was found to have a right lower lobe wedge pressure of 14 mm. Hg. which rose to 16 mm. Hg. with exercise. The mean gradient across the prosthetic mitral valve was 7 mm. Hg. There was no evidence of right or left ventricular failure at rest or exercise. She remained in atrial fibrillation and the digitalis was continued.

In August 1964 an attempt was made at cardioversion which was initially successful after she was given 75 watt seconds of DC electroshock. A month later she was again found to be in atrial fibrillation. During her subsequent clinic visits from 1964 to 1968, she continued to have only mild symptoms of shortness of breath and orthopnea. She remained in atrial fibrillation. She returned in March 1968 for a routine follow-up examination, complaining of weakness. She was found to have a hemoglobin of 7.3 gm.% and was in sinus rhythm. She was admitted to the hospital for an evaluation of the anemia which was found to be a microcytic hypochromic iron deficiency anemia secondary to a bleeding carcinoma of the cecum. A right hemicolectomy and cholecystectomy were performed.

While in the hospital she continued to have sinus rhythm with intermittent episodes of atrial tachycardia with 2:1 block. She was discharged on digitalis and quinidine and continues to have sinus rhythm four months after discharge.

Discussion

Spontaneous reversion of chronic atrial fibrillation to sinus rhythm is unusual. In searching the literature, only six reports of seven cases can be found.[1,2,3,4,5,6] In these reports the arrhythmia had been present for 14 months, 22 months, 37 months, five years, eight years, 16 years, and 28 years. In the present patient atrial fibrillation was documented for 22 years except for a short period following electrical cardioversion four years ago. Intermittent atrial fibrillation cannot be completely excluded but is unlikely.

There are several theories regarding the mechanisms producing atrial fibrillation. These include: (1) single ectopic focus, (2) multiple foci, (3) single circulating wave or the circus theory, (4) multiple and minute re-entries.[7,8,9,10] Atrial fibrillation has long been known to be associated with rheumatic heart disease, particularly with mitral valve lesions. The frequency with which it develops is related to the duration of the disease, the age of the patient, and the size of the left atrium.[11,12] The incidence of atrial fibrillation in mitral stenosis varies from 40% to 50%; with mitral insufficiency it varies from 26% to 75%, depending on the stage of the disease.[11,13,14,15,16]

It is difficult to maintain sinus rhythm after electric cardioversion in patients with mitral valve disease and atrial fibrillation persisting one year or longer. After a period of time the sino-atrial node probably will not begin to discharge on its own. With chronic dilation of the left atrium, anatomic changes occur with the development of increased amounts of connective tissue between the muscle fibers and in the sino-atrial node.[17,18] It is speculated that this process favors the development of arrhythmias because it may allow a re-entry situation to develop.

Following cardioversion from atrial fibrillation to sinus rhythm there may not be effective contractions of the atria.[19,20,21] In our patient it is not certain whether or not effective atrial contractions have occurred, since no "a" waves were seen in the neck. As indicated from the catheterization data in 1964, her wedge pressure is not elevated, and yet the size of the left atrium is

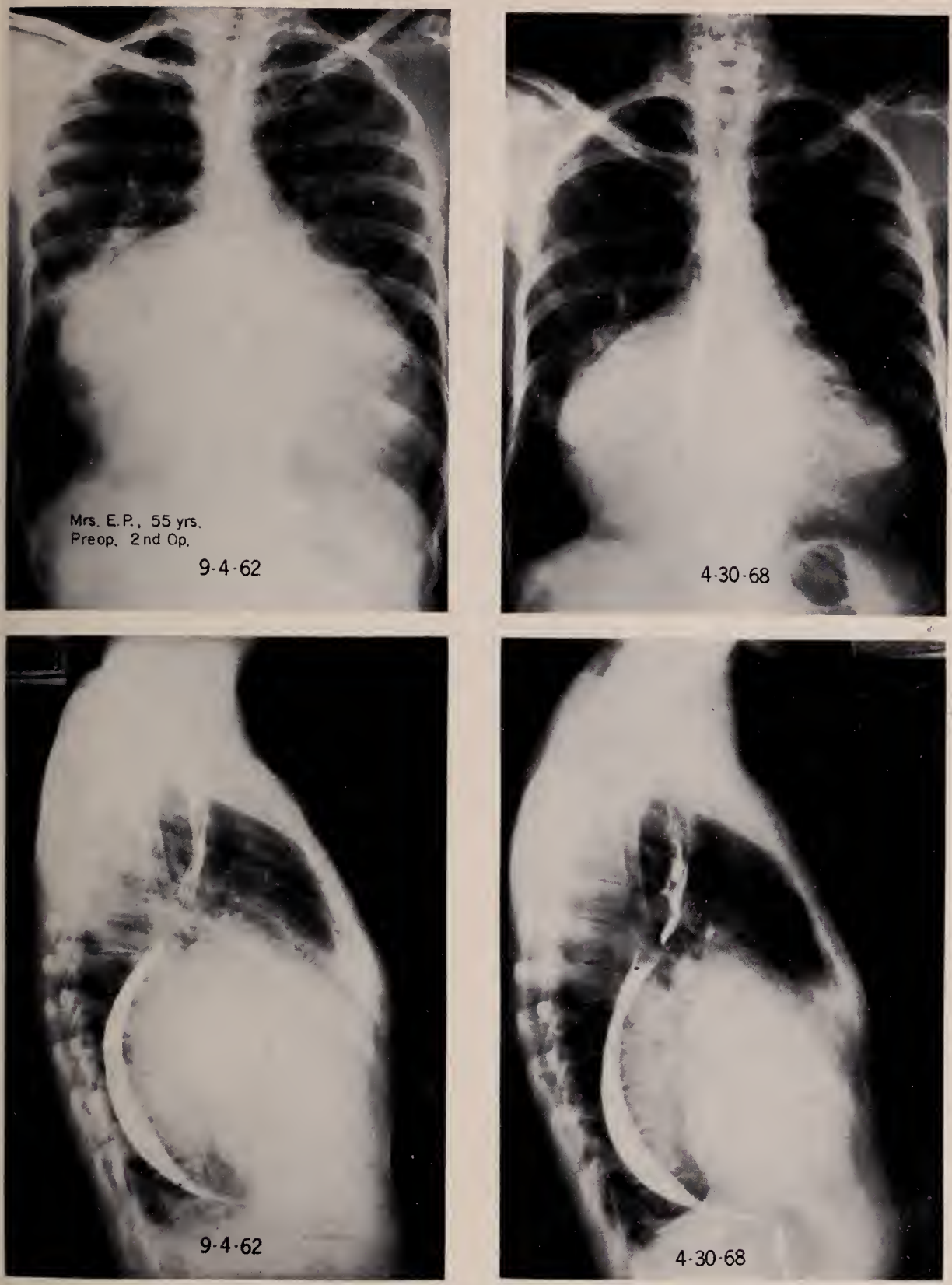


Fig. 3—Posteroanterior and lateral chest x-rays taken prior to surgery in September 1962 (left) and in April 1968 (right).

only slightly smaller than preoperatively (Figure 3).

According to Moe et al.,[22,23] the likelihood of persistence of atrial fibrillation depends on the average number of wavelets present in the atria. This in turn will depend upon the size of the atria, the mean duration of the refractory period, and the conduction velocity.[22] If the average number of wavelets is small enough, there is a chance that they will fall in phase and the arrhythmia will be self-limited. This theory may explain the spontaneous conversion of chronic atrial fibrillation to sinus rhythm.

Summary

A patient with rheumatic heart disease who spontaneously converted from chronic atrial fibrillation to sinus rhythm is presented. The theories as to the etiology of atrial fibrillation, the difficulty in cardioversion of chronic atrial fibrillation, and lack of mechanical contraction of the atria after cardioversion are reviewed. The mechanism of spontaneous conversion of chronic atrial fibrillation is discussed.

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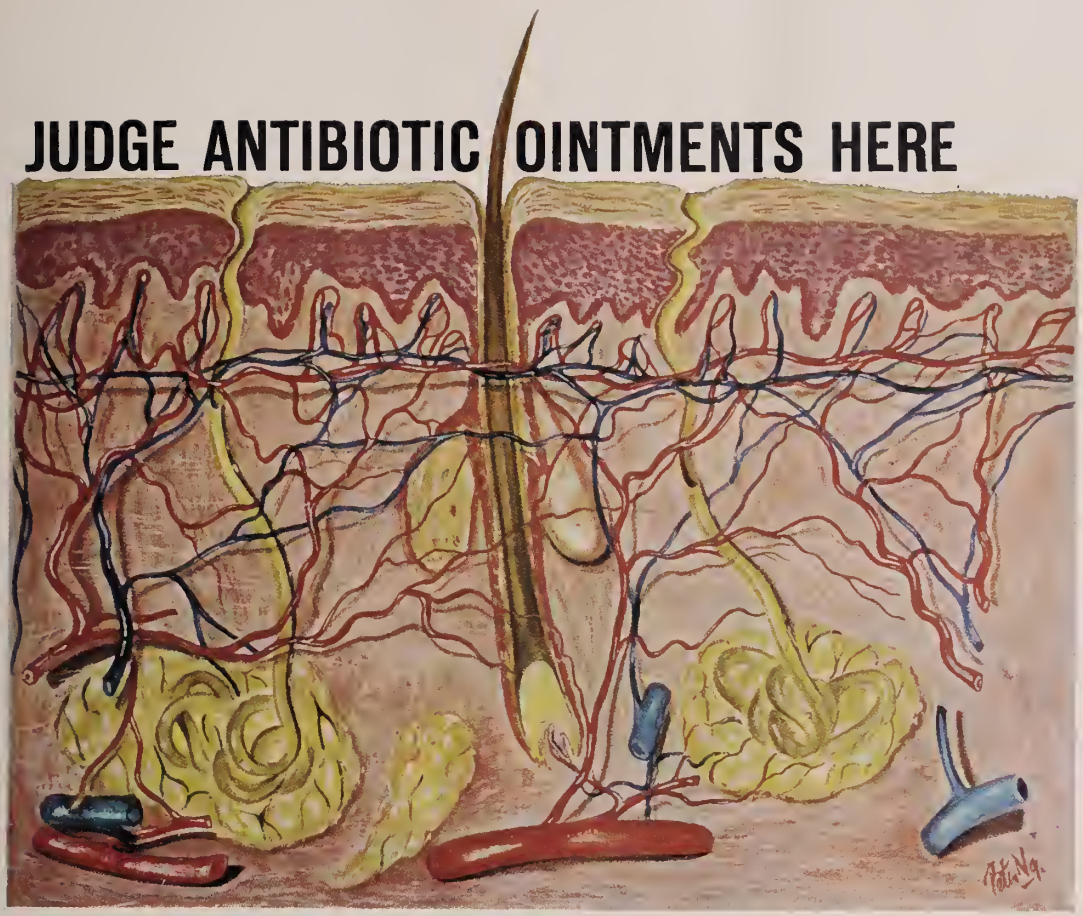
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On Hand Movements

Respecting the movements of the hands I have these observations to make: When in acute fevers, pneumonia, phrenitis, or headache, the hands are waved before the face, hunting through empty space, as if gathering bits of straw, picking the nap from the coverlet, or tearing chaff from the wall—all such symptoms are bad and deadly.*

*From Hippocrates' Book of Prognostics.

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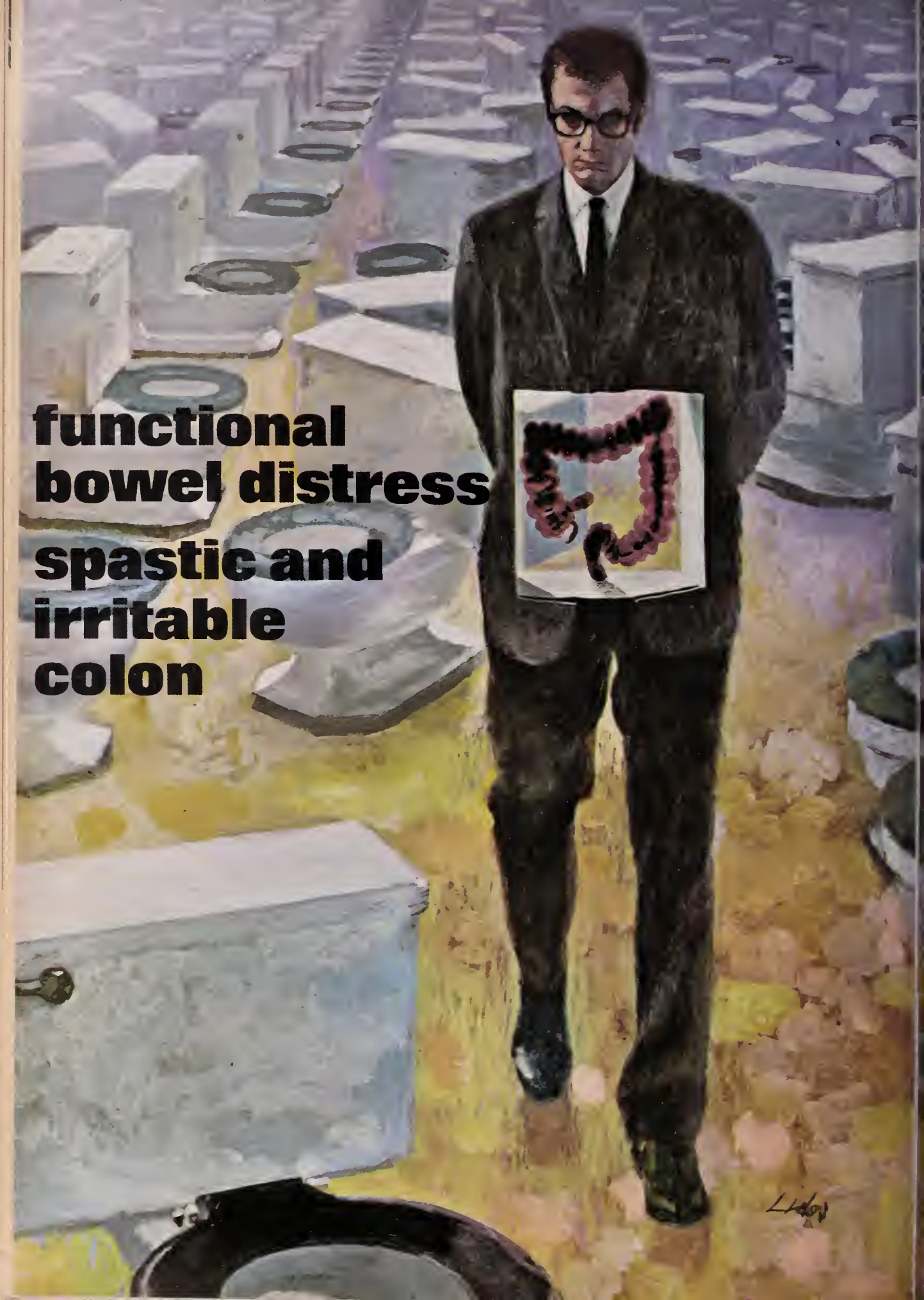
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(Continued to page 580)

Addiction

Opiate Addiction 1971

ROBERT MASLANSKY, M.D.

"Of all the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium." This was written in 1680 by the great English physician, Sydenham. We can modify this aphorism, inserting the words "and add to" between "to relieve" and "his sufferings."

Chemistry of Opium and its Derivatives

Papaver somniferum, a plant indigenous to semi-tropical areas of the earth, is the source of the milky exudate from which opium powder is extracted. The phenanthrene derivatives are the analgesically active alkaloids: the two principal ones being morphine and codeine. Semi-synthetic modification of morphine and codeine results in diacetylmorphine (heroin) and Hydromorphone (dilaudid) when the alcoholic OH group is oxidized and hydrogenation removes the adjacent double bond. Another group of potent narcotic analgesics are the so-called opioids. Structually unlike naturally occurring and semi-synthetic alkaloids these chemicals have the same analgesic and, for the most part, the same central nervous system effects as the opiate alkaloids and their semi-synthetic congeners. The two opioids commercially available are methadone (dolophine) and meparidine (demarol). The pharmacology of these drugs is well known. The mechanism of action at the intracellular and synaptic level has not been clearly worked out. Recent work indicates that affective changes associated with these drugs are related to the changes in the concentration of the brain serotonin.

Street Use of the Opiates

Narcotic addicts, well-grooved into the so-called junky subculture, disdain the synthetic opioid demerol. From the street addict's point of view there is little difference between diacetylmorphine and hydromorphine (heroin and dilaudid). Many addicts complain that using the parent compound morphine intravenously causes an unwanted "pins-and needles feeling" which is distressing.

The connoisseur addict can state with authority his preference for one or another of these drugs; but challenging the addict to distinguish the naturally-occurring and semi-synthetic alkaloids shows that such discrimination is not always possible.

Of the many reported side effects of the legitimate and appropriate use of opiate drugs, addicts add a few observations of their own. Universally, male addicts report, but not necessarily complain of, reduced or ablated libidinous drive. Street use of opiate drugs, however, can be titrated so as to permit sexual performance on an intermittent basis. This is done by partially withdrawing from the drug, permitting the libidinous urge and capacity to return for a short time. Bowel and bladder difficulties frequently noted are often home-remedied by using large quantities of cathartic. A voluminous literature has developed on the inordinate susceptibility to a variety of unusual infections. Not a few cases of right-sided sub-acute bacterial endocarditis have been reported. Homologous serum jaundice is frequently considered a subcultural merit badge. Tetanus and malaria are also seen.

Prototypes of Addicts

No one knows the number of opiate abusers there are in Minnesota. Estimates range from 1,000 to 4,000. Several prototypes can be identified, however. One is a male, about 25, coming from a socially disorganized and deprived background, most characteristically having an ineffectual or absent father and a pathologically-dominant mother. The pathogenesis of this prototype is reasonably clear. Ordinarily the patient has been poorly adjusted to school prior to his

first acquaintance with narcotic drugs. At the age of 16, as a result of peer-group pressure, he becomes acquainted with the narcotizing effects of codein in a cough syrup mixture. Previously, his relationship to chemical abuse may have been episodic drunkenness, again as a manifestation of peer group pressure. Use of codein cough syrup ultimately leads to mild physical dependence.

At this juncture, the first brush with the law occurs. If a suspended sentence is issued, then the individual is remanded to one of the Federal treatment centers at Fort Worth or Lexington. Within six months he becomes an accomplished and knowledgable user of opiates. With the help of fellow inmates, the novitiate is taught many things: techniques for extracting opium from suppositories, the distinction between the sundry types of opiate drugs, the proper way to find an elusive vein. He has also learned a value system which disdains a meaningful relationship with regular (square) society. He learns to substitute hustle for legitimate work. After release a more intense physiologic dependency develops which serves to reinforce this increasing identification with a special brand of living: the junky subculture. Drug seeking becomes a total commitment; dangerously asocial activities associated with drug seeking are very quickly learned. Practice makes for considerable skill in these special techniques for money making, e.g., shoplifting, till tapping, burglary, armed robbery, prostitution, etc.

The second prototype is the spouse of an addict. It is evident from observing this group that this disorder is highly contagious even in a relatively resistant population. These addicts as a rule do not show significant psychopathology, but by virtue of their contiguity to their user spouse or lover, they very rapidly acquire as pernicious and as persistent a habit.

Thirdly, there is a relatively small group of professional addicts, most of whom do not constitute a social problem because of the facility with which they can maintain their addiction and the ease with which they can hide it.

Finally, there is the hippie becoming an addict, following a path from hallucinogens to intravenous amphetamines and then opiate. The opiates serve to "put my head together," say these young people, and, indeed, in most ways they are quite right. There is little doubt that the opiates will . . . assuage the mind-blowing disruptive effects of amphetamines, but at the cost of addiction.

Economics of Opiate Distribution

In this community, the concept of a czar of narcotics distribution is mythic; here, universally, the seller is the user. Indeed, there are not a few users who are very occasional sellers, but there are no sellers who are not users. The marketing of the narcotic here follows two flow routes. Illicit heroin is brought into the Minneapolis-St. Paul area by the user-seller in small shipments from Chicago, Montreal, the California cities and New York. Very little jobbing is done here on heroin: possibly one cut of a 1:1 ratio. Though quality varies considerably on the street, the average #5 capsule filled with heroin averages 3.5 to 4 mg. of pure material. The diluent is ordinarily quinine or one of the non-barbiturate sedatives such as glutethimide. A single capsule sells for $10.00. A man with a very strong physical dependence can use as many as 10 capsules a day.

The other route of distribution is the so-called "drugstore stuff." This is material either burglarized from drugstores or otherwise illegitimately obtained through forged prescriptions or robbed doctors' bags. Another source for this illegal narcotic are legitimately-filled prescriptions written by physicians who have taken compassion on the narcotic user and supplied him with prescriptions to be filled on a regular basis, theoretically for his own use but, in fact, in most instances, for resale on the street. Quality control of his material is built in and an unequivocal dealer-consumer relationship can be established. Nothing is more highly prized than uncracked ampules of dilaudid. These also sell for approximately $10.00. Of course, as in all other commodities, there is market variation, as drugs respond to the laws of supply and demand.

A very special place is reserved for cocaine in the armamentarium of the addict. Cocaine is a non-addicting stimulant drug when used parenterally, with central nervous system action similar to large doses of a sympathomimetic amine. Interestingly, it was first described for parenteral use by Sigmund Freud in the treatment of endogenous depression, but it was very quickly abandoned because of its undesirable side effects

and extremely short duration. In the junky subculture, cocaine is used in a spree-like fashion. There is no addicting liability to it. It is used parenterally in the setting of a communal relationship. It has a marked physiologic effect, not dissimilar to an orgasm. Ordinarily, an addict will repetitively inject cocaine at $10.00 a shot until all of his money is gone, or until he becomes so fatigued and at the same time so stimulated that he can no longer tolerate the drug.

The Rational Approach to Therapy

As in the treatment of other chronic disorders, one can structure a hierarchy of goals in the treatment of the addict. Ideally we would want all addicted individuals to become law-abiding, emotionally mature, contributing members to society. More especially, we would want them to become drug clean. These expectations, however, we do not insist upon with any other group of chronically ill individuals. We certainly do not expect the patient with mild congestive heart failure to become an Olympic runner or to abandon digitalis, diuretics or visits to his physician. The minimum expectation is that the drug user, under treatment, give up illicit activity associated with drug seeking. Beyond this, we can structure other goals for him which may include the maintenance of the abstemious state. For special physiologic and social reasons it has been discovered over the years that the abstemious state is unmaintainable in approximately 95% of all addicts placed in it. Thus it would be rational to offer many a continuous modality of therapy which would include social redirection and rehabilitation. Such a modality is methadone maintenance. Regrettably, under the provisions of the Harrison Narcotic Act, there continues to be some legal question as to the appropriateness of this form of therapy. There is no question but that strict safeguards must be maintained in offering continuous therapy.

Parenthetically, other treatment programs that have high virtue with respect to the idealized form of therapy, that is, maintenance of the abstemious state, must not preclude methadone maintenance as an alternative. The law must be cognizant of the dealer-user relationship. It must have a special concern for the highest orders of distribution, the entrepreneurial dealer who is a non-user. The dealer-user should be looked at differently and handled as a special problem. Basically, what this means is that all users of narcotics must be considered patients with an illness that is remarkably amenable to certain types of therapy. The law should not preclude the medical treatment of an addict with the kind of therapy that is most appropriate for his particular condition.

From A Doctor's Journal

April 1, 1898.

I had a peculiar experience yesterday and last night. A man came for me about 7.30 in the morning and wanted me to go to his house in a hurry. I had not finished dressing but I hurried and was there in about 25 minutes, but a boy was born before I got there.

About half past ten p.m. another man came and wanted me to go to his house in a hurry. I dressed quickly and was at his house in about 20 minutes, but a boy was born before I got there.

About 1 this a.m. a man came to the house and thought he might want me to go to his house soon. I advised him to go back and if he needed me I would go quickly. He returned soon and I was at his house before two o'clock. But before I reached his house *two* boys were born.*

*David S. Kellogg, M.D.: A Doctor at All Hours, 1970. Edited by Allan Everest.

It is the bounty of nature that we live, but of philosophy that we live well.—Seneca



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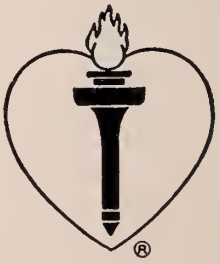
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Clinical Path Conference

Cystitis and Carcinoma of the Bladder

Dr. Alexander S. Cass[†]**:** Dr. Vitko will present the case.

Dr. Roger Vitko:[‡]

This 66-year-old man presented on August 5, 1968 with urinary frequency and dysuria for three weeks but with a good stream.

Physical examination was normal except for a slightly enlarged, smooth, nontender prostate gland. Urinalysis revealed 1+Wbc (4-8/HPF) and 2+Rbc (8-30/HBF). Urine culture was sterile. Chest x-ray and intravenous pyelogram were both normal. Voiding cystourethrogram and retrograde urethrogram were

*Urology Department, St. Paul-Ramsey Hospital, St. Paul, Minnesota.

†Chief, Department of Urology, St. Paul-Ramsey Hospital.
‡Urology Resident, St. Paul-Ramsey Hospital.



Fig. 1—Cystogram showing irregularity of bladder wall.

also normal. Cystoscopy showed a normal bladder, but there was purulent discharge from the prostatic ducts. A diagnosis of prostitis was made, and the patient was treated with antibiotics.

Over the next three months his symptoms worsened, with frequency every hour and nocturia six times. Urinalysis revealed 3+ red cells (30-50/HPF), 2+ Wbc. Urine culture grew Streptococcus fecalis. A Mantoux test and repeated urine cultures for tubercle bacillus were negative. An intravenous pyelogram showed normal upper tracts, but the bladder outline had some irregularity on the left side with a thick bladder wall (Figure 1). A voiding cystourethrogram revealed a small bladder capacity.

Dr Edward Richardson:*

The irregularity of the bladder wall on the left side is not normal and should arouse suspicion of some type of bladder pathology.

Dr. Vitko:

Cystoscopy at this time, November 7, 1968, revealed a reddened mucosa of the entire bladder and cystitis cystica in one area of the bladder. Multiple biopsies with the resectoscope were obtained and showed chronic inflammation with a focus of cells which was highly suspicious for malignancy (Figure 2).

Dr. Stanley Antolak:*

What do you think should have been done now that the biopsies revealed chronic inflammation, one focus which was suspicious of malignancy, and a bladder outline on IVP and cystogram showing irregularity on the left side?

Dr. Gerald W. Ireland:*

In discussion and slide review with the pathologists, the written report on a focus of cells of malignancy was not firmly held; so it was felt that further biopsies should be taken after a short period of treatment to resolve the infection.

*Urologist, Department of Urology, St. Paul-Ramsey Hospital

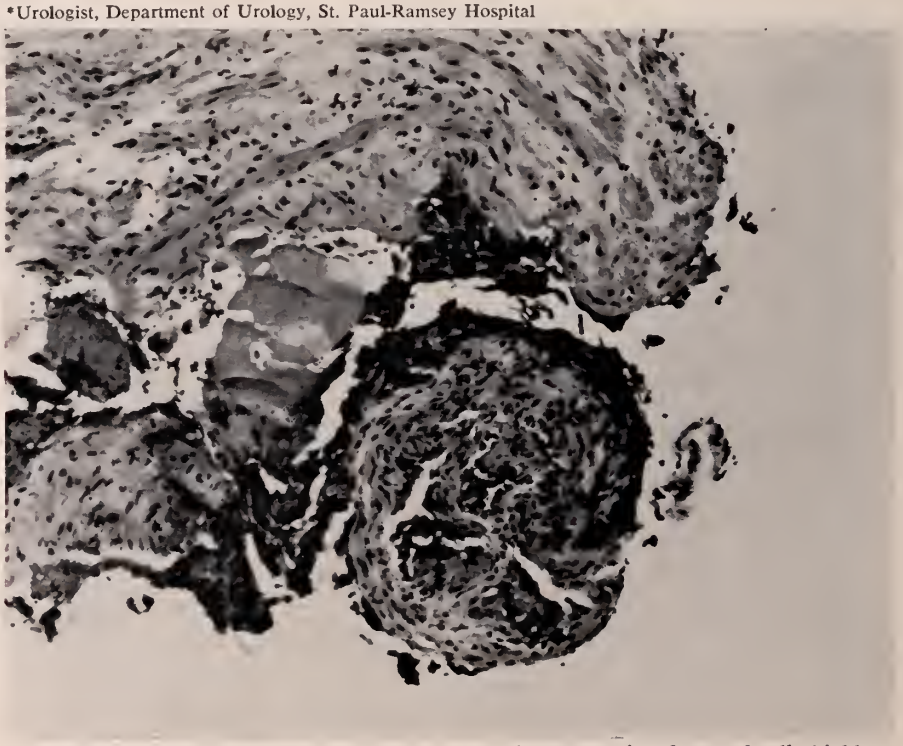


Fig. 2—Photomicrograph of original bladder biopsy showing focus of cells highly suggestive of malignancy.

Dr. Vitko:

After antibiotic treatment for one month, the patient was cystoscoped, with findings of diffuse reddening of the bladder mucosa and areas of cystitis cystica. Multiple resectoscope biopsies were taken, which revealed only chronic inflammation (Figure 3). These were thoroughly reviewed with the pathologists.

For the next three months the patient had no relief of symptoms. Physical examination remained normal. Urinalysis showed 3+ red cells, 2+ Wbc. Urine culture again grew Streptococcus fecalis. Urological x-rays demonstrated only the small contracted bladder. Cystometrogram showed a bladder capacity of 150 ml. with a strong micturition reflex. The patient was given eight intravenous doses of Mepharsen, 40 mg, I.V., at weekly intervals as an empirical treatment for cystitis.

Dr. Richardson:

The diagnosis was now chronic cystitis, and Mepharsen was advocated occasionally for the treatment of abacterial pyuria. In this case we have infection with Streptococcus fecalis.

Dr. Vitko:

At the end of this treatment, the patient developed gross hematuria as well as continued frequency and nocturia. Urine culture again grew Streptococcus fecalis. Cystoscopy revealed a reddened edematous mucosa in the dome, but the mucosa of the bladder base appeared normal.

Dr. Richardson:

The presence of gross hematuria following the previous microscopic hematuria has now contributed a great factor for concern in the diagnosis of this man's trouble. Everything adds up to chronic cystitis, but malignancy must also be suspected.

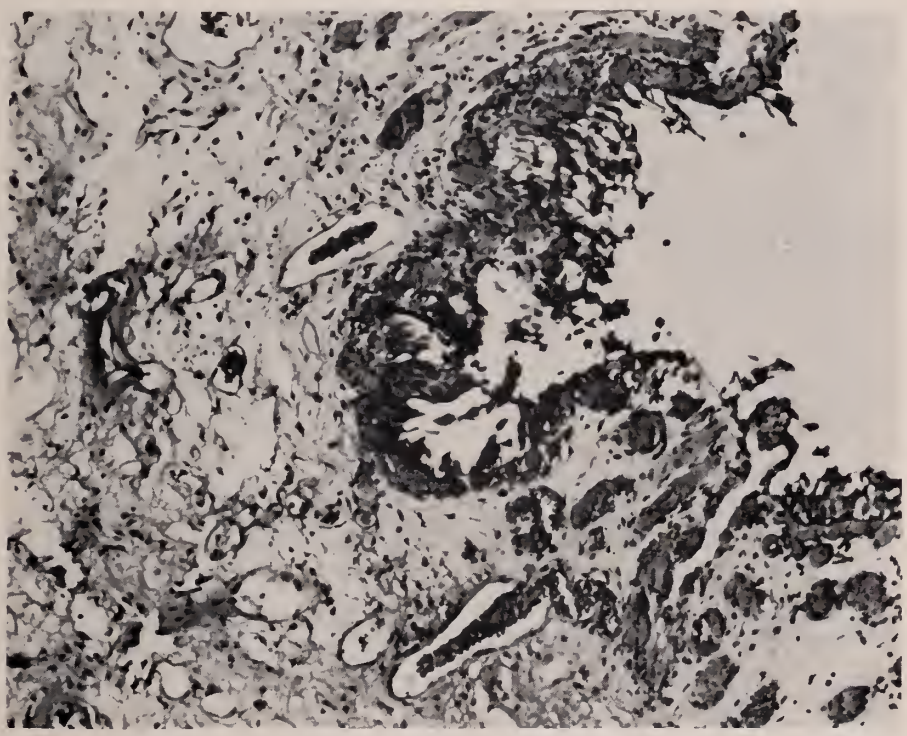


Fig. 3—Photomicrograph of repeat bladder biopsy one month later showing chronic inflammation only.

Dr. Ireland:

At this stage consideration was given to cystectomy, as the patient's symptoms were severe and disabling. Because of the continued presence of Streptococcus fecalis in the urine, efforts were made to demonstrate a vesico-intestinal fistula.

Dr. Antolak:

I feel further attempts should have been made to arrive at a positive diagnosis without delay.

Dr. Vitko:

The patient's symptoms continued with frequency every 15 to 30 minutes. Urinalysis showed 2+ Wbc, 3+ Rbc. Urine culture grew Streptococcus fecalis. He was given oral charcoal, and the urine was examined in an effort to diagnose a vesico-colic fistula; no granules were seen. Barium enema and proctoscopy were normal. Urine for tubercle bacillus was negative. Chest x-ray was normal (Figure 4). For his chronic cystitis he was given a trial of steroids, which did not improve his symptoms. It was now 10 months since he had been first seen. A diversion was discussed with the patient because of his severe symptoms, and a final cystoscopy and bimanual examination were carried out. The examination revealed no masses or fixation; the cystoscopy still showed a reddened bladder mucosa. Bladder biopsies were again taken which demonstrated Grade III transitional cell carcinoma with submucosal infiltration (Figure 5).

Dr. Cass:

The presentation of this carcinoma of the bladder was most likely masked as a chronic cystitis for almost one year. What is the relationship of cystitis and carcinoma of the bladder?

Dr. Antolak:

I think this entire case presents an interesting evaluation of the problem of



Fig. 4—Normal chest roentgenogram

continuing cystitis or prostatitis in the male, which too frequently would be treated with only prostatic massage and antibacterial therapy. I think you are to be commended for continuing the workup with so many cystoscopies and biopsies. The tragedy is that we didn't have positive biopsies or continuing biopsies earlier. The changes in the bladder suggest that the bladder wall is thickened on the early pyelograms, and a little irregularity on the left side of the dome might make you consider this a cystitis with a perimural type of inflammation. One should also consider some associated bowel problem. However, your bimanual examination would be very important here as I think you would have felt any perivesical abscess or phlegmon at the time of the initial cystoscopy. Also, the mucosa originally appeared normal, which one certainly wouldn't suspect in a diverticulitis with involvement of a portion of the bladder.

So I think the first diagnosis you made, namely prostatitis, may well have been correct. We can't really tell in this series when the carcinoma actually started or if it was present at this time. If we were to see a carcinoma following chronic cystitis, I should think we would observe it much more frequently in females or in children with reflux and chronic cystitis. However, I have seen a few patients who, I am sure, have developed a bladder malignancy after long-standing infections. I think, in retrospect, that, with a questionable first diagnosis of malignancy, not definitely confirmed by the pathologists, the whole process was malignant from the beginning, but was masked by cystitis.

Dr. Gerald McEllistrem:*

The only thing I can add with relation to chronic inflammation is that I have seen a case of leukoplakia which, after many years, developed into a carcinoma. I think there is a relationship between leukoplakia and carcinoma of the bladder,

*Urologist.



Fig. 5—Photomicrograph of repeat bladder biopsy 7 months later showing Grade III transitional cell carcinoma with submucosal infiltration.

as well as on other epithelial surfaces.

Dr. Ireland:

There are irritants or carcinogenic agents that have been known for years to result in bladder tumors, particularly among workers involved with chemicals. aniline dyes and plastics. Beta-napthylamine and Xenylamine are carcinogenic. cinogenic.

Also recently, there have been reports of a high incidence of bladder carcinoma in workers in the rubber industry, but the exact agent here has not been identified.

Finally, there is a clear relationship between carcinoma of the bladder and infestation of the bladder by Schistosoma haematobium. Roughly 5-10 percent of these cases develop carcinoma.

Our patient did not work in the rubber industry or with chemicals and had never been out of the United States.

Dr. Antolak:

Well, I think it is interesting that he had been known to be a heavy smoker, because of the correlation that some people, especially Kerr in Toronto, make with cigarette smoking and carcinoma of the bladder. Kerr found that cigarette smokers had a higher output of urinary carcinogenic metabolites of tryptophan. When they stopped smoking this level dropped.

Dr. Richardson:

Doctor Kerr recently reported trying to reproduce bladder cancer in mice, using tryptophan. The original work was done by implanting paraffin pellets impregnated with tryptophan metabolites into mouse bladders, thus producing bladder cancer.

When Kerr inserted the paraffin alone, it produced just as many bladder cancers as the combination of paraffin and tryptophan. However, direct injection by Dr. Kerr of tryptophan alone in a series of animals failed to produce the cancer.

Dr. Cass:

What treatment would you now propose?

Dr. McEllistrem:

The choices of treatment, I think, would be: (1) radical cystectomy and urinary diversion, or (2) radiation therapy. I believe there is a debate among not only urologists but other specialists as well as to the best type of treatment. The radiotherapists have produced some fairly good results in recent years with cobalt therapy. My personal feeling is that cobalt therapy is a good modality of treatment. The patient can be reevaluated some three months later; then, if carcinoma is still present, one can consider radical cystectomy.

Dr. Richardson:

Personally I do not think that cobalt is indicated in this case; the patient has a small contracted bladder with a lot of irritation and would be no better, and probably worse symptomatically, after the course of cobalt therapy.

Dr. McEllistrem:

There are several series of preoperative irradiation procedures prior to cystec-

tomy. After radical cysteetomies, 20 to 30 percent of these bladders had no evidence of carcinoma. Since they showed a 20 to 30 percent cure from the cobalt therapy, I think preoperative cobalt is a good idea.

Dr. Antolak:

I had a recent conversation regarding a referral to Dr. Matthews of the Radiation Therapy Department here. He agrees that it is very diffieult to "sterilize" bladder carcinoma. He does not feel that this is a good total therapy in many instances but should be used as an adjunct to surgery for carcinoma of the bladder.

Just a note that in cancer of the cervix, irradiation of the pelvis does not kill all tumor cells in the pelvic lymph nodes; at later surgery viable tumor cells are often found in the pelvic lymph nodes.

Dr. Ireland:

In general, with more malignant and invasive tumors, we have to choose between radiotherapy and radical surgery. Some Centers are using combinations: preoperative radiation to 2500 rads or higher and then radical cystectomy at six to eight weeks. Some propose postoperative radiation. The preoperative factors that correlate with long-term survival are the degrees of cellular differentiation and of infiltration. With invasion over half way through the bladder wall curability decreases sharply. It was our impression from biopsy and bimanual examination that we did not have deep invasion but that the cell type was a Grade III.

Dr. Vitko:

The patient underwent a radical cystectomy, a pelvic lymphadenectomy and an ileal diversion on July 10, 1969. The specimen of the bladder revealed carcinoma with only submucosal infiltration (Fig. 6). All the lymph nodes from the pelvis were



Fig. 6—Photomicrograph of tumor from cystectomy specimen showing infiltrating Grade III carcinoma. Additional sections did not show invasion of muscularis.

negative for metastasis. The patient did well for six months and then developed a fever and cough (January 1970). Examination showed a normal functioning ileal diversion. Chest x-ray revealed a right upper lobe consolidation, and planograms of the right upper lobe showed obstruction of the right upper lobe bronchus (Figure 7), confirmed by bronchoscopy. A right supraclavicular node was palpable. A biopsy of the right node and histopathology revealed anaplastic carcinoma (Figure 8).

Dr. Ireland:

The diagnosis was questionable: whether it was a metastasis from the carcinoma of the bladder or a new malignancy in the form of carcinoma of the lung with a metastasis to the right supraclavicular node. The pathologists were unable to be dogmatic.

Dr. Vitko:

The patient was given 2500 rads to the right upper chest area over a two-week period in an effort to shrink the malignancy and remove the obstruction of the right upper lobe bronchus. Two weeks later he showed no improvement on his chest x-ray. His persistent cough continued and he was given a course of Prednisone, 50 mg. q.d., in an effort to relieve any possible edema, but he obtained no relief from this treatment. He was then given chemotherapy in the form of Cytoxan, 7.5 mg/kg/day I.V., for four days and, after a rest period of one week, was given Methotrexate, 10 mg. twice a week, and a weekly dose of Cytoxan between 100-200 mg., depending on the Wbc and platelet count. This was continued for three months on an outpatient basis. There was some transient improvement, but this was followed by an extension of the atelectasis in his right side to the right middle lobe. The patient became acutely dyspneic on June 17, 1970, and rapidly expired.



Fig. 7—Chest roentgenogram taken 6 months postoperatively, showing consolidation of upper lobe of right lung.

Dr. Antolak:

Something should be said about the refractory nature of the transitional cell tumors to any means of chemotherapy. Although there has been some response by the low-grade lesions with topical Thio-tepa, little progress has been made in treatment of infiltrative lesions with a combined sort of regimen that was used here. One might consider whether preoperative, operative, or immediate postoperative therapy might be tried, such as using actinomycin D with embryonal cell carcinoma of the kidney or now, as some surgeons are doing, with carcinoma of the breast. If there are any metastatic cells or tumor emboli the best chance of eliminating them is when the number of mass tumor cells is small.

Dr. Cass:

The disappointing feature here was that a man who had a radical cystectomy in which the pathology revealed only submucosal infiltration of the carcinoma with negative pelvic nodes had such a poor result. Could anyone comment from his own experience on the course of this type of carcinoma of the bladder which presents as a chronic cystitis with malignant change over the whole bladder?

Urology Staff:

No comment.

Dr. Cass:

Any further comments on carcinoma of the lung versus carcinoma of the bladder with metastasis to the lung?

Dr. Richardson:

My choice is carcinoma of the bladder with metastasis.

Dr. Vitko:

The autopsy revealed that the right lung weighed 2,200 grams, the left lung

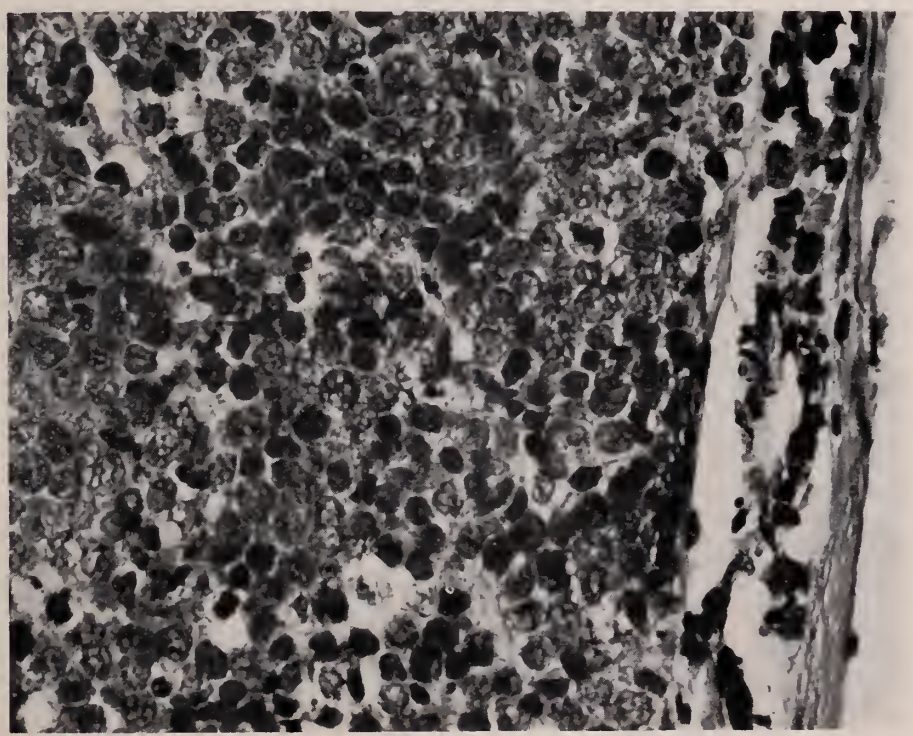


Fig. 8—Photomicrograph of right supraclavicular node showing anaplastic carcinoma.

330 grams. The right lung was massively replaced by tumor, the cut section revealing a firm white tumor mass in the hilar region extending out and involving almost the entire upper portion of the lung. The adrenal gland showed involvement of small whitish tumor nodules. The diversion was intact, well healed and functioning. Section of the kidneys showed normal cortical medullary architecture, with the renal pelves and ureters normal. The iliac nodes were not palpable and there was no evidence of residual tumor in the pelvis. The para-aortic nodes were involved by a whitish, fleshy tumor extending from the level of the inferior mesenteric artery up to and including the mediastinum at the level of the supraclavicular region. The mediastinum was densely matted with a massive tumor in the region of the superior mediastinum with some compression of the mediastinal structures.

The cause of death was respiratory insufficiency.

Anatomic Diagnosis: Carcinoma of the bladder with metastasis to the para-aortic nodes, mediastinal nodes, left adrenal gland and right lung.

On Wine In Acute Diseases

One must determine when sweet, strong, and dark wine should be given in acute diseases. Wherefore the sweet affects the head less than the strong, attacks the brain less, evacuates the bowels more than the other, but induces swelling of the spleen and liver; it does not agree with bilious persons, for it causes them to thirst; it creates flatulence in the upper part of the intestinal canal, but does not disagree with the lower part, as far as regards flatulence; and yet flatulence engendered by sweet wine is not of a transient nature, but rests for a long time in the hypochondria. And therefore it in general is less diuretic than wine which is strong and thin; but sweet wine is more expectorant than the other. But when it creates thirst, it is less expectorant in such cases than the other wine, but if it does not create thirst, it promotes expectoration better than the other. The good and bad effects of a white, strong wine, have been already frequently and fully stated in the disquisition on sweet wine; it is determined to the bladder more than the other, is diuretic and laxative, and should be very useful in complaints; for if in other respects it be less suitable than the other, the clearing out of the bladder effected by it is beneficial to the patient, if properly administered. There are excellent examples of the beneficial and injurious effects of wine, all which were left undetermined by my predecessors. In these diseases you may use a yellow wine, and a dark austere wine for the following purposes: if there be no heaviness of the head, nor delirium, nor stoppage of the expectoration, nor retention of the urine, and if the alvine discharges be more loose and like scrapings than usual, in such cases a change from a white wine to such as I have mentioned, might be very proper. It deserves further to be known, that it will prove less injurious to all the parts above, and to the bladder, if it be of a more watery nature, but that the stronger it is, it will be the more beneficial to the bowels.*

*Hippocrates

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History

A Physician by the Name of Ohiyesa

Charles Alexander Eastman, M.D.

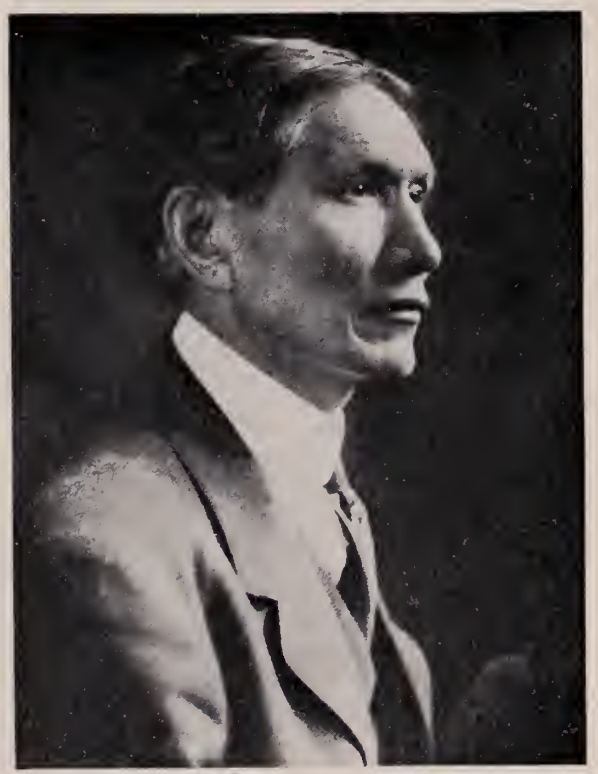
THOMAS W. MILROY, M.D.*

In the late winter of 1858 near Redwood Falls, Minnesota Territory a dying Indian mother gave birth to her fifth child, a boy, who later, as a man, would distinguish himself as physician, author, lecturer and leader of his people. However, until the boy could earn a more dignified name he had to bear the name "Hakadah," meaning "the pitiful last."

About four years later this lad was given a name to be proud of: one that foretold his future success and was determined by a lacrosse† contest. To the camp of Mankato or Blue Earth on the Minnesota River, several bands of the eastern Dakotas had come for midsummer contests and festivities. This season the most important event was the lacrosse game between the Kaposia and the Wahpeton bands. With about fifty players on each side, what a contest this must have been! After a long struggle the Wahpetons were victorious when one of their players carried the ball across the opponents' goal line. To the victors went the privilege of giving a new name to one of their worthy little warriors. At a ceremony following the game the little boy, Hakadah, was brought to the center of the circle and received the name Ohiyesa: winner, or one who advances.

But for the Santee Dakotas a time of tragedy had already begun and was soon to be shared by the white settlers in the bitter conflict known as the Sioux Uprising of August 1862, instigated by starvation and implemented by many grievances. In 1851, the Indians had been persuaded to cede most of their land for ten cents an acre, but the annual interest had not been paid for two years. Nor had necessary supplies been received. After the uprising was crushed the Dakotas were pursued westward until they found temporary refuges across the Missouri River and in Canada. With his family, Ohiyesa was among those who went to Canada. There his father, Many Lightnings, and two elder brothers were betrayed, delivered over to United States authorities, returned to the United States, and sentenced to death. Fortunately, Ohiyesa was not with his father and brothers at the time of their capture; he was staying with his uncle, Mysterious Medicine, and remained with him for the next ten years. While roaming the wilderness of southern Manitoba, he grew up learning to be a hunter and a warrior, vowing to return to avenge the supposed execution of his father and brothers.

However, a new period of Ohiyesa's life was



Charles Alexander Eastman, M.D.

*Student Health Service, University of Minnesota.

†Lacrosse—an Indian game resembling football or basketball, in which a ball is maneuvered by a racket or crosse into the opponents' goal.

about to begin. On one eventful day in September 1872 his father arrived at the camp and was reunited with his son. Ohiyesa learned that, due to the intervention of President Lincoln, his father had not been hanged but had, instead, been imprisoned at Davenport, Iowa, for four years. There he had been converted to Christianity and had taken the name Jacob Eastman. Some time after his release he brought his son back to a new homestead at Flandreau, Dakota Territory, in order that Ohiyesa could start school and begin to learn the ways of civilization. Subsequently, Ohiyesa became known as Charles Alexander Eastman.

In 1872, a very reluctant pupil began the studies that he would pursue with increasing interest and distinction for the next 18 years. He attended a one-room country school near his home for two years. Then in the fall of 1874 he walked 150 miles to the mission boarding school at Santee, Nebraska. During the next two years he was influenced to accept Christianity and to pursue further study by the Reverend John P. Williamson and by the superintendent, Dr. Alfred Riggs.

For the next five years, with the help of Dr. Riggs, he was able to continue his studies at Beloit College, Wisconsin, and at Knox College, Galesburg, Illinois. After a year of further preparation at Kimball Union Academy, he entered the freshman class at Dartmouth College in 1883 and received his B.S. degree in 1887. There he was captain of the class of 1887 football team and was an outstanding athlete, particularly in long-distance running. His next three years were spent at Boston University where he received his M.D. degree in 1890.

In October of that year Dr. Eastman began his medical career as government physician at Pine Ridge Agency, South Dakota. Prior to his coming, all medicines had been passed out to Indian patients through a hole in the wall of the dispensary, like a ticket seller's window. His first official act was to close up this hole and have his patients come inside for an examination before treatment.

He had come at a time of mounting tension and apprehension. Spreading among the Indians was the ghost dance religious movement: a new cult which promised the Indians that their messiah would destroy the cities of the white men with earthquakes, famine and pestilence. While awaiting this holocaust, the Indians were taught that they should live by themselves, fast, pray, and perform a certain spirit dance. But the white settlers and the government officials feared that this would lead to another Indian uprising. At Standing Rock Agency the Indian police were ordered to arrest Chief Sitting Bull on December 15. In the fight that ensued he and some of his men and police were killed. On December 29 a number of Indians, encamped near Wounded Knee Creek, were surrounded by troops of the Seventh Cavalry and ordered to surrender their weapons. A search for rifles was undertaken, and soon the shooting began. In the massacre that followed nearly 300 Indians were killed, most of them unarmed men, women, and children.

That night about 64 wounded Indians and soldiers were brought to Pine Ridge, where the mission chapel was quickly converted to a hospital under the direction of Dr. Eastman. Two days later, after a blizzard had subsided, Dr. Eastman led a rescue party to search for survivors. Among the bodies they found in the snow some were still alive. They were brought back and a few survived.

Assisting Dr. Eastman at this time, as a volunteer nurse, was his fiancee Elaine Goodale. She had already spent three years among the Dakota Indians as a pioneer teacher and had become supervisor of Indian schools in Nebraska and the Dakotas. The two had met shortly after his arrival at Pine Ridge and were soon engaged. On June 18, 1891, they were married in New York City.

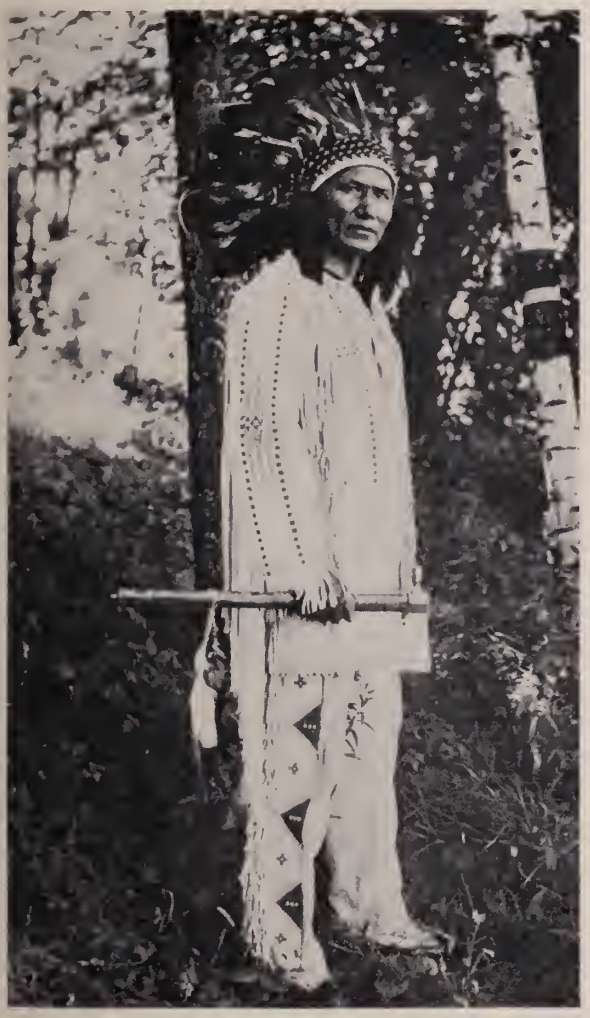
Dr. Eastman and his bride returned to Pine Ridge Agency and moved into their new home in the fall of 1891. However, they were not destined to have a lifetime of service there, as they had hoped. That fall when the annual treaty money was paid to the Indians, a bitter dispute arose over shortages in the payments. An additional $100,000 was to have been paid as compensation for the losses suffered during the previous year by Indians who had not joined the ghost dance movement. No counting was permitted at the time of the rapid distribution of the payments, and it was not long before angry complaints arose. Dr. Eastman and others were convinced that the Indians had been cheated out of about $10,000. An apparently farcical investigation cleared the officials. Then all who had not

concurred with the agent were forced to leave.

Dr. Eastman moved to St. Paul, Minnesota, early in 1893. He was licensed in July and spent the next few months in establishing a private medical practice.

About this time the International Committee of the Y.M.C.A. was looking for a suitable man to help extend their program among the Indians of the western part of the United States and Canada, and Dr. Eastman was persuaded to enter their service. For the next three years, he traveled extensively, visiting mission stations among Indians of all tribes in this area and organizing about 43 new associations.

Responding to the need for a representative of the Dakotas in Washington, D.C., he moved there in 1897. During three sessions of Congress he endeavored to obtain a settlement of various claims and a restoration of the treaty payments that had been withheld after the 1862 Minnesota Uprising.



Ohiyesa

Then for a four-year period Dr. Eastman again became a government physician in the Indian Service, spending one year at Carlisle, Pennsylvania, and the next three years at Crow Creek Agency, South Dakota.

In 1903 Dr. Eastman was appointed by President Roosevelt to undertake the revision of the Dakota allotment rolls. Over a period of seven years, he personally interviewed many hundreds of the Dakotas to determine family groups and to establish family surnames. Family names were needed to protect the inheritance of property, and they had to be names that could be easily pronounced or translated into English.

During these years Dr. Eastman was also becoming widely acclaimed as an author and a lecturer. His first book, *Indian Boyhood,*[1] was published in 1902. In the next 16 years, nine more books[2-10] followed, the last being *Indian Heroes and Great Chieftains* in 1918. His books and published articles[12,14] have provided a permanent and authentic description of the traditions, folklore and religion of the Dakota Indians in their original free state. He also described the serious health problems and deplorable living conditions of reservation life.[8]

Soon after his first book was published, Dr. Eastman was invited to speak in Brooklyn, N.Y. Thereafter he was persuaded to give more lectures, and then found himself in demand as a lecturer for the rest of his life. In 1911 he gave an address[13] at the First Universal Races Congress in London, England, where he represented the North American Indian. In 1927 he returned to England to lecture at Oxford, Cambridge and other British universities.

Appointed by President Coolidge, Dr. Eastman served as United States Indian Inspector from 1923 to 1925.

Throughout his life, Dr. Eastman was an advocate of camping and outdoor recreation. He helped organize the Boy Scouts of America and also the Camp Fire Girls in Boston, New York City, Pittsburgh, and other cities. With the help of his wife, and usually several of their six children, he conducted a private camp in New Hampshire for several years. In later life he spent the summers at his cabin on the north channel of Lake Huron.

Dr. Eastman died in Detroit, January 8, 1939, at the age of 81. During his lifetime he received many honors and awards. It is now apparent that his memory will continue to be honored and that his scholarship will serve as an example for present and future generations. A $3,000 fellowship for American Indian students entering first-year medical school has been established by the Association on American Indian Affairs and the Mead Johnson Laboratories: very appropriately named The Charles Eastman Fellowship.*

Dr. Eastman's life and character exemplified many of the finest qualities of the American Indian and of the "Christ ideal"[9] which he accepted as a young man: the courage to accept new challenges and the determination to advance to successive heights of achievement.

How eminently this native American lived up to his distinguished name of Ohiyesa!*

*Also, the Dr. Charles Ohiyesa Eastman Scholarship Inc. 1620 Maryland Avenue South, St. Louis Park, Minnesota 55426 has recently been formed to aid American Indian students in any of the health professions in Minnesota.

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School of Salerum II

Sharpe *Choller* is an humour most pernitious,
All violent, and fierce, and full of fire,
Of quicke conceit, and therewithall ambitious,
Their thoughts to greater fortunes still aspire,
Proud, bountifull ynough, yet oft malicious
A right bold speaker, and as bold a lyar,
On little cause to anger great enclin'd,
Much eating still, yeat ever looking pin'd:
In younger years they use to graw apace.
In Elder hairie on their brest and face.

Editor's note: As for the choleric man: the School excoriates him a bit too unmercifully. Tall, gaunt and hairy, he is a physiological anomaly: he can eat voraciously without getting fat, probably wearing it off in his tantrums. His one positive characteristic of generosity can hardly compensate for his inordinate ambition, irascibility, malice and mendaciousness. He is caricatured as beating his wife.

Four Varieties

Upon the first goblet he read this inscription: monkey wine; upon the second, lion wine; upon the third, sheep wine: upon the fourth, swine wine. These four inscriptions expressed the four descending degrees of drunkeness: the first, that which enlivens; the second, that which irritates; the third, that which stupifies; finally the last, that which brutalizes.*

*Victor Hugo (1802-1885) as quoted in A Mirror up to Medicine by A. C. Corcoran, M.D., 1961.

In Memoriam

Let us cross the river and rest in the shade.—General "Stonewall" Jackson

LEON A. BARNEY, M.D.

Dr. Leon A. Barney, 86, practicing physician in Duluth for 46 years, died December 13. A native of River Falls, Wisconsin, Dr. Barney was a graduate of the University of Minnesota Medical School and interned at St. Mary's Hospital in Duluth.

He had served for 14 years before his retirement as port surgeon for the U. S. Public Health Service, treating merchant seamen in Duluth and was also a former chief of surgeons at St. Mary's Hospital. Dr. Barney was a member of the St. Louis County Medical Society and the American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

Dr. Barney is survived by his son and a daughter.

CHARLES H. DECKER, M.D.

Dr. Charles H. Decker, 55, St. Paul physician for 30 years including 15 years as a deputy county coroner, died December 3.

A native of Duluth, Dr. Decker came to St. Paul in 1940 to become deputy coroner and was associated with the Northern Pacific Hospital. From 1956 until his death, he was a general practitioner associated with St. Joseph's and St. Luke's hospitals. He was a member of the Ramsey County Medical Society, the American Medical Association, and the Minnesota State Medical Association.

Dr. Decker is survived by his wife, four daughters and six sons.

SAMUEL AMBERG, M.D.

Dr. Samuel Amberg, one of the founders of the modern specialty of diseases of children, and internationally known as an authority in that field, died November 29. He was born in Cannstatt, near Stuttgart, Western Germany, and received the degree of doctor of medicine from the University of Heidelberg. He came to the United States in 1899. In 1921, he came to the Mayo Clinic and remained there until his retirement in 1946.

He was certified as a specialist in pediatrics, was a fellow of the American Academy of Pediatrics, and a member of the American Medical Association, the American Physiological Society, the American Pharmacological Association, the American Biochemical Association, the Society of Experimental Biology and Medicine, the Northwestern Pediatric Society, the American Pediatric Society, the Society of the Sigma XI and the Alumni Association of the Mayo Graduate School of Medicine. He was a corresponding member of the Viennese Society of Internal Medicine, member of the Zumbro Valley Medical Society, and a Life and 50 Club Member of the Minnesota State Medical Association.

EDWARD W. OSTERGREN, M.D.

Dr. Edward W. Ostergren, 85, St. Paul surgeon, died November 25. Born in St. Paul, Dr. Ostergren received his medical degree from the University of Minnesota.

He was voted "Outstanding General Practitioner of Ramsey County" in 1948 and was a member of the Phi Beta Pi Fraternity, the American Medical Association, Ramsey County Society, a fellow of the American College of Surgeons and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife, two daughters, Doctors Eva Jane Larson and Lenore Nimlos, and brother, Dr. Daniel O. Ostergren.

ORVIE J. SWENSON, M.D.

Dr. Orvie J. Swenson, 72, Waseca physician and coroner, died November 26. Three years of premedical work and one year of medicine was completed at the University of Iowa before transferring to the University of Minnesota where he received his medical degree.

He was a member of the American Medical Association, the Minnesota State Medical Association, the Southern Minnesota and Waseca County Medical Societies, Minnesota Academy of General Practitioners, elected to Alpha Omega Alpha Honorary Fraternity, and held membership in several Masonic bodies.

Dr. Swenson is survived by a daughter, and his son, Dr. Donald Swenson of Mankato.

WALTER F. KVALE, M.D.

Dr. Walter F. Kvale, 63, former head of the section of medicine at the Mayo Clinic, died November 25. Born at Orfordville, Wisconsin, he moved to Rochester in 1934 as a fellow in medicine of the Mayo Graduate School of Medicine, after receiving his medical degree from Northwestern University.

In 1940 he was appointed consultant in a section of medicine and was head of the section from 1957 to 1958. He authored or co-authored some 80 publications, and for fifteen months prior to his retirement he was a member of the Section of Environmental Medicine. He advanced in academic rank to professor of medicine.

Dr. Kvale was a member of the American Medical Association, the Zumbro Valley Medical Society and the Minnesota State Medical Association.

He is survived by his wife, four sons and a daughter.

O. WILLIAM HOLCOMB, M.D.

Dr. Oscar William Holcomb, 93, a practicing St. Paul physician and surgeon for 44 years, died November 19. Born in rural Chisago County and a graduate from Northwestern University Medical School, Dr. Holcomb began his practice in St. Paul in 1907, retiring in 1951. He received a degree of Ph.G. in 1898 from the Minnesota Institute of Pharmacy before entering medical school.

He was a fellow of the American College of Surgeons, a member of the American Medical Association and Ramsey County Medical Society and a Life and 50 Club Member of the Minnesota State Medical Association. He was also a past president and member of the St. Paul Surgical Society and the Ramsey County Medical Society, and former Chief-of-Staff of Bethesda Hospital. Dr. Holcomb was a member of the Minnesota State Board of Health and the Alpha Omega Alpha Honorary Medical Fraternity.

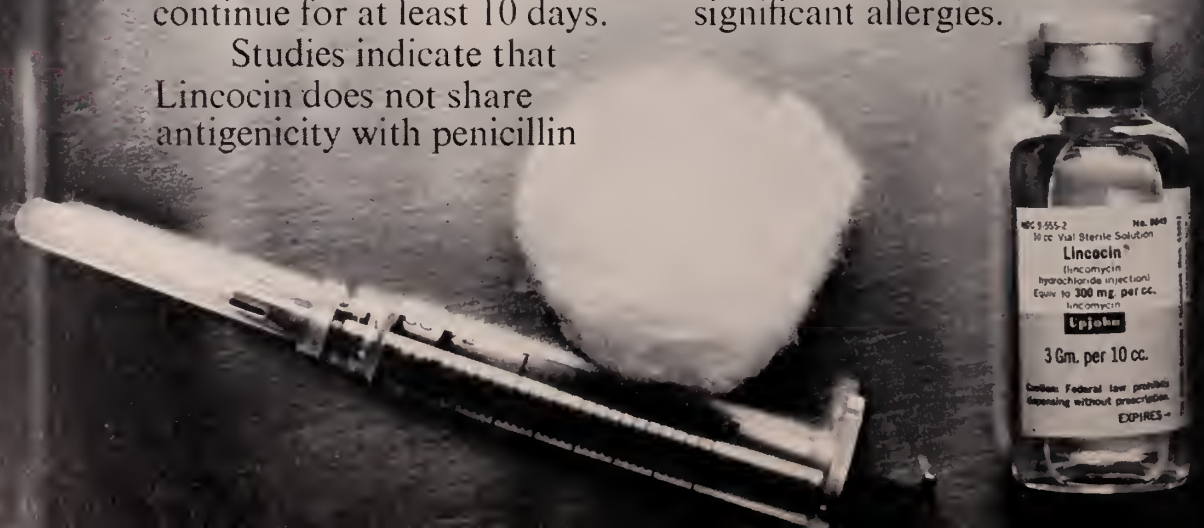
He is survived by his wife, Dr. John E. Holcomb of Hopkins, his son, another son, an attorney and his brother, Dr. Joel T. Holcomb, Marine-on-St. Croix.

Hypersensitivity to penicillin is a good reason to consider Lincocin®

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Lincocin (lincomycin hydrochloride, Upjohn) has produced a high percentage of satisfactory responses in patients with mild, moderate and severe infections due to susceptible streptococci, pneumococci and staphylococci (including many penicillinase-producing strains). With β-hemolytic streptococcal infections, treatment should continue for at least 10 days.

Studies indicate that Lincocin does not share antigenicity with penicillin compounds. However, hypersensitivity reactions such as angioneurotic edema, serum sickness and anaphylaxis have been reported, some of these in patients known to be sensitive to penicillin. As with any antibiotic, Lincocin (lincomycin hydrochloride, Upjohn) should be used cautiously in patients with histories of asthma or other significant allergies.



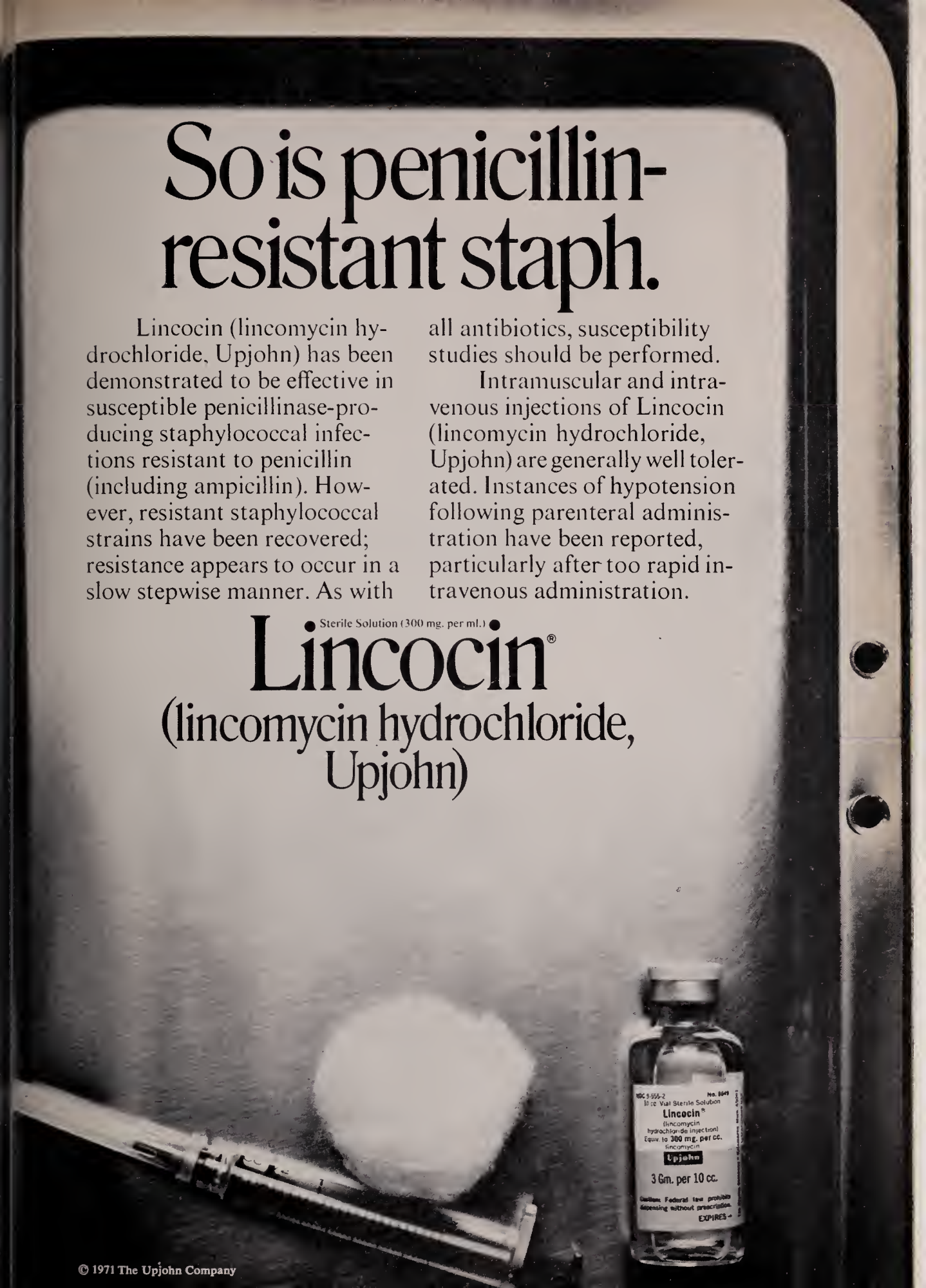
So is penicillin-resistant staph.

Lincocin (lincomycin hydrochloride, Upjohn) has been demonstrated to be effective in susceptible penicillinase-producing staphylococcal infections resistant to penicillin (including ampicillin). However, resistant staphylococcal strains have been recovered; resistance appears to occur in a slow stepwise manner. As with all antibiotics, susceptibility studies should be performed.

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Lincocin®

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Each preparation contains:	Lincomycin hydrochloride monohydrate equivalent to lincomycin base
250 mg. Pediatric Capsule	250 mg.
500 mg. Capsule	500 mg.
*Sterile Solution per 1 ml.	300 mg.
Syrup per 5 ml.	250 mg.

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CONTRAINDICATIONS: History of prior hypersensitivity to Lincocin (lincomycin hydrochloride). Not indicated in the treatment of viral or minor bacterial infections.

WARNINGS: Cases of severe and persistent diarrhea have been reported and at times drug discontinuance has been necessary. This diarrhea has been occasionally associated with blood and mucus and at times has resulted in acute colitis. This reaction usually has been associated with oral therapy, but occasionally has been reported following parenteral therapy. Although cross sensitivity to other antibiotics has not been demonstrated, make careful inquiry concerning previous allergies or sensitivities to drugs. Safety for use in pregnancy has not been established and Lincocin is not indicated in the newborn. Reduce dose 25 to 30% in patients with severe impairment of renal function.

PRECAUTIONS: Like any drug, Lincocin should be used with caution in patients having a history of asthma or significant allergies. Overgrowth of nonsusceptible organisms, particularly yeasts, may occur and require appropriate measures. Patients with pre-existing monilial infections requiring Lincocin therapy should be given concomitant antimonilial treatment. During prolonged Lincocin therapy, periodic liver function studies and blood counts should be performed. Not recommended (inadequate data) in patients with pre-existing liver disease unless special clinical circumstances indicate. Continue treatment of β-hemolytic streptococci infection for ten days to diminish likelihood of rheumatic fever or glomerulonephritis.

ADVERSE REACTIONS: *Gastrointestinal*—Glossitis, stomatitis, nausea, vomiting. Persistent diarrhea, enterocolitis, and pruritus ani. *Hemopoietic*—Neutropenia, leukopenia, agranulocytosis, and thrombocytopenic purpura have been reported. *Hypersensitivity reactions*—Hypersensitivity reactions such as angioneurotic edema, serum sickness, and anaphylaxis have been reported, sometimes in patients sensitive to penicillin. If allergic reaction occurs, discontinue drug. Have epinephrine, corticosteroids, and antihistamines available for emergency treatment. *Skin and mucous membranes*—Skin rashes, urticaria, vaginitis, and rare instances of exfoliative and vesiculobullous dermatitis have been reported. *Liver*—Although no direct relationship to liver dysfunction is established, jaundice and abnormal liver function tests (particularly serum transaminase) have been observed in a few instances.



Cardiovascular—Instances of hypot sion following parenteral administrat have been reported, particularly after t rapid I.V. administration. Rare instan of cardiopulmonary arrest have been ported after too rapid I.V. administrati If 4.0 grams or more administered I dilute in 500 ml. of fluid and adminis no faster than 100 ml. per hour. *Lo reactions*—Excellent local tolerance de onstrated to intramuscularly administer Lincocin. Reports of pain following jection have been infrequent. Intra nous administration of Lincocin in 2 to 500 ml. of 5% glucose in distill water or normal saline has produced local irritation or phlebitis.

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Book Reviews

Laws die. Books never.—Bulwer-Lytton

ATLAS AND DIAGNOSTIC TECHNIQUES AND TREATMENT OF INTRAOCULAR FOREIGN BODIES. William H. Havener, M.D. and Sally L. Gloeckner, M.A. C. V. Mosby Company. Price: $19.50.

Intraocular foreign bodies are fortunately not a common occurrence in the ordinary ophthalmologic practice. When they do occur, however, they are all of serious import and require skilled and mature management. Dr. Havener has written an excellent text pertinent to the management of intraocular foreign bodies. The book is divided into two parts, the first being diagnostic techniques and the second, extraction techniques. Precise details of diagnosis and extraction are fully and logically presented.

Some of the diagnostic techniques discussed include ophthalmoscopy, gonioscopy, posterior segment biomicroscopy. In addition to these direct methods of examination the more specialized techniques of the use of the Berman locator, ultrasound and x-ray localization are discussed.

In the section on extraction techniques the details of extraction from the anterior chamber, posterior chamber and lens are discussed. Attention is also given to the extraction of foreign bodies far posteriorly, and there is information pertinent to repair of scleral laceration, the handling of nonmagnetic foreign bodies, retinal detachments, the use of cryotherapy and photocoagulation.

The book has many and very useful diagrams by Sally L. Gloeckner, medical illustrator, of Ohio State University. Dr. Havener, who is a professor of ophthalmology at Ohio State University, in conjunction with the same illustrator has published priorly (1967) a book called "Atlas of Diagnostic Techniques and Treatment of Retinal Detachment." The present volume could well be considered a companion volume to the earlier book, as the problems of retinal detachment and intraocular foreign bodies are so intertwined. Some necessary and useful overlap information in the two atlases is noted.

The "Atlas of Diagnostic Techniques and Treatment of Intraocular Foreign Bodies" presents in a single source a complete approach to its subject material. The atlas is hard-bound, totals 197 pages inclusive of index and, as noted before, is well illustrated. It is published by the C. V. Mosby Company and is highly recommended to all ophthalmologists.

Irving Shapiro, M.D.
Minneapolis, Minnesota

ACHALASIA OF THE ESOPHAGUS. F. Henry Ellis, Jr., M.D., Ph.D. (Surgery), F.A.C.A. and Arthur M. Olsen, M.D., M.S. (Medicine), F.A.C.P. W.B. Saunders Company, Philadelphia, London, Toronto.

This monograph on achalasia has been written by two masters of their subject whose knowledge and expertise in this field are unsurpassed. The book is dedicated to Norman R. Barrett whom the authors call the "Doyen of Esophageal Surgery." Dr. Engelbert Dunphy writes in the Foreword that it will remain the authoritative work on achalasia for many years to come. He is unquestionably right.

This work consists of nine chapters, including history, pathogenesis, physiology (written by Code and Schlegel), clinical features and diagnosis, roentgenology of achalasia, nonsurgical and surgical treatment; a full chapter is devoted to the development of a rational surgical approach. In tabulating the operative results in the last chapter the authors not only drew on their own extensive experience at the Mayo Clinic but tediously collected a great number of operative series from all over the world. The references throughout the book are altogether pertinent and almost unbelievably complete and accurate.

In spite of its completeness this monograph is never dull and gives the reader the pleasant illusion of listening to a very interesting and grand lecture by the Professor himself. This I believe to be the ingredient of an excellent medical text, and I recommend it warmly to every interested physician.

H. W. Heupel, M.D., Ph.D.
Minneapolis, Minnesota

COLOR ATLAS AND TEXTBOOK OF HEMATOLOGY. William R. Platt, M.D., Assistant Professor of Pathology, Washington University, School of Medicine, St. Louis, Missouri. Pages 445. Color Plates 73. J. B. Lippincott, Philadelphia, 1969. Price $27.00.

The purpose of this Color Atlas and Textbook of Hematology, the successor to Krake's Color Atlas of Hematology, is to enhance the proficiency of the clinical pathologist, medical technologist, and hematology supervisor to learn and teach morphologic differentiation of bone marrow and peripheral blood cells.

Most color photographs lack sharpness, and the Wright's stained cells have a confusing kaleidoscopic color diversity. Background colors of plate figures range from pink, blue, brown, to green. Drying, fixing and staining artefacts are prevalent. Several of the plates are water-color pictures; these reveal clearly that the artist is not a trained cellular morphologist.

Contents of the book include Origin and Development of Blood Cells, Clinical Laboratory Procedures, Quality Control, Automatic Methods, Bone Marrow Biopsy, Electron Microscopy, Chromosome Abnormalities, Hematologic Disorders, and Therapy. Carnoy's fixative formula has an omission error. Bibliography and references to audiovisual aids appear at the end of each chapter.

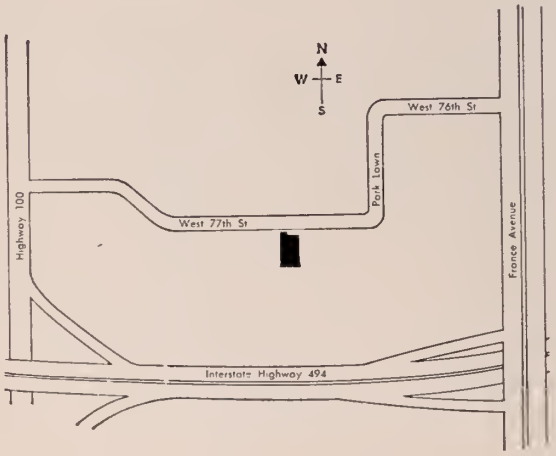
This Color Atlas-Textbook is not the most desirable addition to the clinical laboratory teaching library, but it has sufficient merit to be recommended as an auxiliary reference work.

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Indications
Pre-Sate (chlorphentermine hydrochloride) is indicated in exogenous obesity, as a short term (i.e. several weeks) adjunct in a regimen of weight reduction based upon caloric restriction.

Contraindications
Glaucoma, hyperthyroidism, pheochromocytoma, hypersensitivity to sympathomimetic amines, and agitated states. Pre-Sate (chlorphentermine hydrochloride) is also contraindicated in patients with a history of drug abuse or symptomatic cardiovascular disease of the following types: advanced arteriosclerosis, severe coronary artery disease, moderate to severe hypertension, or cardiac conduction abnormalities with danger of arrhythmias. The drug is also contraindicated during or within 14 days following administration of monamine oxidase inhibitors, since hypertensive crises may result.

Warnings
When weight loss is unsatisfactory the recommended dosage should not be increased in an attempt to obtain increased anorexigenic effect, discontinue the drug. Tolerance to the anorectic effect may develop. Drowsiness or stimulation may occur and may impair ability to engage in potentially hazardous activities such as operating machinery, driving a motor vehicle, or performing tasks requiring precision work or critical judgment. Therefore, such patients should be cautioned accordingly. Caution must be exercised if Pre-Sate (chlorphentermine hydrochloride) is used concomitantly with other central nervous system stimulants. There have been reports of pulmonary hypertension in patients who received related drugs.
Drug Dependence Drugs of this type have a potential for abuse. Patients have been known to increase the intake of drugs of this type to many times the dosages recommended. In long-term controlled studies with the high dosages of Pre-Sate, abrupt cessation did not result in symptoms of withdrawal.
Usage In Pregnancy The safety of Pre-Sate (chlorphentermine hydrochloride) in human pregnancy has not yet been clearly established. The use of anorectic agents by women who are or who may become pregnant, and especially those in the first trimester of pregnancy, requires that the potential benefit be weighed against the possible hazard to mother and child. Use of the drug during lactation is not recommended. Mammalian reproductive and teratogenic studies with high multiples of the human dose have been negative.
Usage In Children Not recommended for use in children under 12 years of age.

Precautions
In patients with diabetes mellitus there may be alteration of insulin requirements due to dietary restrictions and weight loss. Pre-Sate (chlorphentermine hydrochloride) should be used with caution when obesity complicates the management of patients with mild to moderate cardiovascular disease or diabetes mellitus, and only when dietary restriction alone has been unsuccessful in achieving desired weight reduction. In prescribing this drug for obese patients in whom it is undesirable to introduce CNS stimulation or pressor effect, the physician should be alert to the individual who may be overly sensitive to this drug. Psychologic disturbances have been reported in patients who concomitantly receive an anorectic agent and a restrictive dietary regimen.

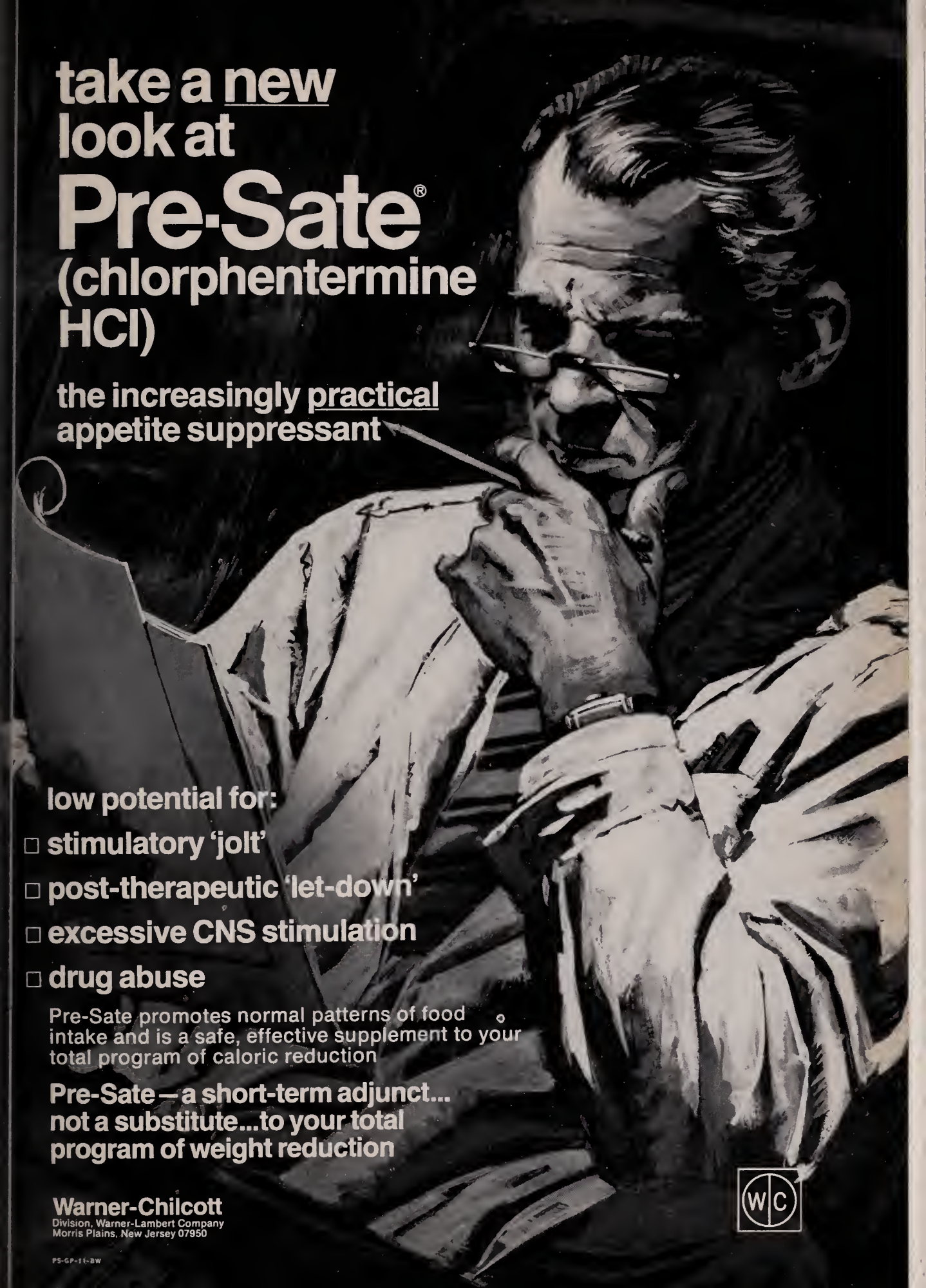
Adverse Reactions
Central Nervous System: When CNS side effects occur, they are most often manifested as drowsiness or sedation or overstimulation and restlessness. Insomnia, dizziness, headache, euphoria, dysphoria, and tremor may also occur. Psychotic episodes, although rare, have been noted even at recommended doses. **Cardiovascular:** tachycardia, palpitation, elevation of blood pressure. **Gastrointestinal:** nausea and vomiting, diarrhea, unpleasant taste, constipation. **Endocrine:** changes in libido, impotence. **Autonomic:** dryness of mouth, sweating, mydriasis. **Allergic:** urticaria. **Genitourinary:** diuresis and, rarely, difficulty in initiating micturition. **Others:** Paresthesias, sural spasms.

Dosage and Administration
The recommended adult daily dose of Pre-Sate (chlorphentermine hydrochloride) is one tablet (equivalent to 65 mg chlorphentermine base) taken after the first meal of the day. Use in children under 12 not recommended.

Overdosage
Manifestations: Restlessness, confusion, assaultiveness, hallucinations, panic states, and hyperpyrexia may be manifestations of acute intoxication with anorectic agents. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension, or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.
Management: Management of acute intoxication with sympathomimetic amines is largely symptomatic and supportive and often includes sedation with a barbiturate. If hypertension is marked, the use of a nitrate or rapidly acting alpha-receptor blocking agent should be considered. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

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Each Pre-Sate (chlorphentermine hydrochloride) tablet contains the equivalent of 65 mg chlorphentermine base; bottles of 100 and 1000 tablets.

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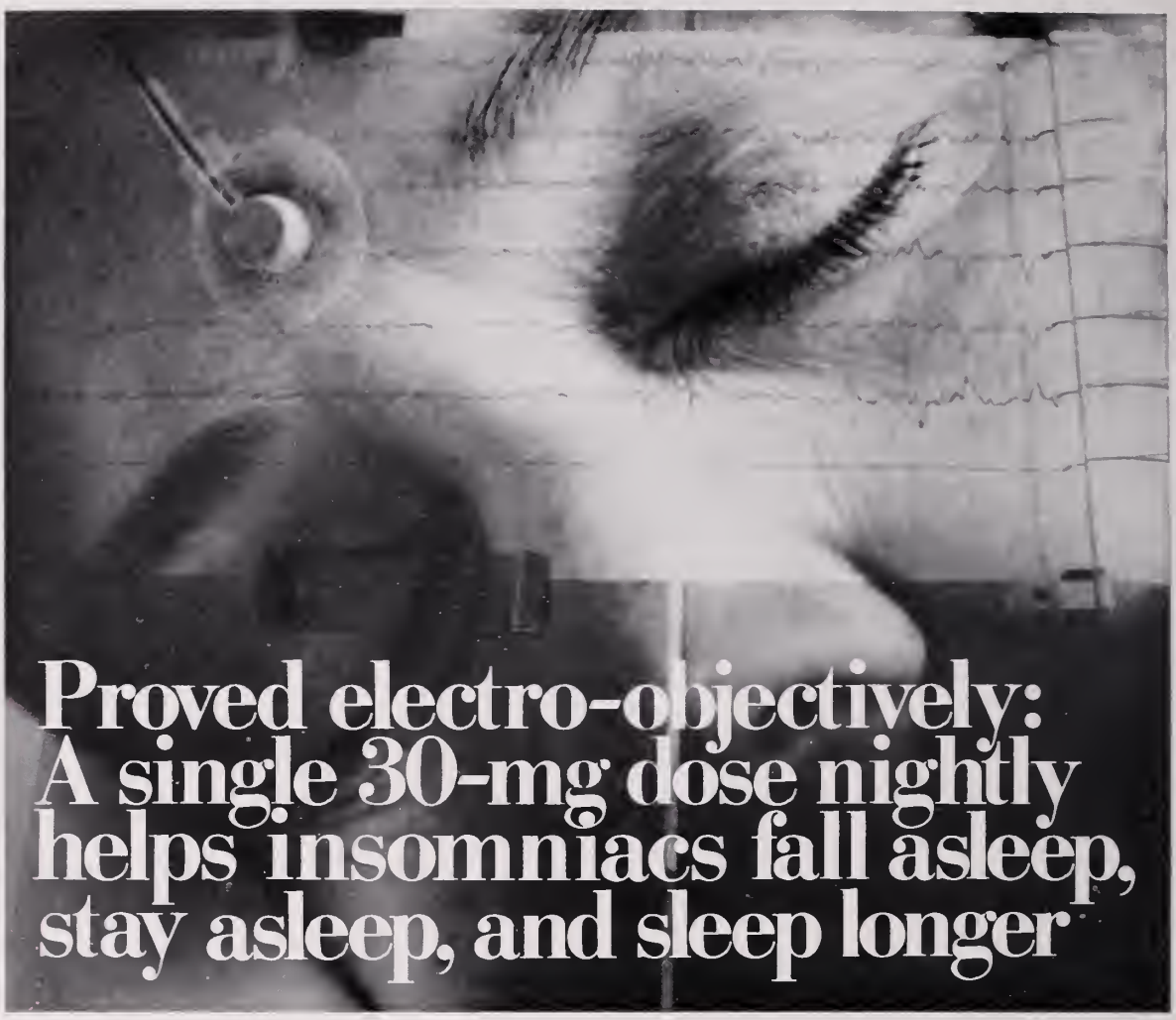
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AUGUST, 1971



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Controlled studies of 23 insomniac and 13 normal subjects treated with Dalmane (flurazepam HCl) in five sleep laboratories generated over 4000 hours of electroencephalographic, electro-oculographic and electromyographic tracings. These studies revealed that Dalmane 30 mg nightly usually induces sleep in 22 minutes and provides seven to eight hours of sleep.[1,2,3]

Moreover, Dalmane 30 mg was found to be useful in all common types of insomnia in which it was studied. Of drugs studied in a sleep laboratory,[1] Dalmane 30 mg was the only one that consistently reduced sleep induction time and maintained sleep nightly for 14 consecutive nights of use.

Confirmed clinically

Fifty-three controlled studies using a paired-night, double-blind crossover design have evaluated Dalmane clinically. In the majority of these, Dalmane (flurazepam HCl) significantly reduced sleep induction time and increased sleep duration. Dalmane and a placebo were alternated on successive nights in 2010 insomniacs, 1706 of whom were studied for a single night-pair, and the remainder for as many as fifteen paired-nights. A patient preference for Dalmane was apparent in the paired-night studies.

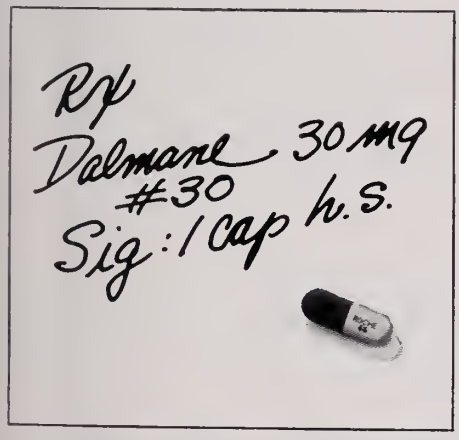
Dalmane was also preferred to certain hypnotics in two separate preference studies. In each of two double-blind studies, Dalmane 30 mg retained effectiveness for the total period of seven consecutive treatment nights, according to subjective/objective evaluations.

In summary, Dalmane is useful in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening. It can be used effectively in patients with recurring insomnia or poor sleeping habits, and in acute or chronic medical situations requiring restful sleep.

Dalmane (flurazepam HCl) is generally well tolerated

In most instances in which adverse effects with Dalmane were reported, they were mild, infrequent and seldom required discontinuation of the drug. Dizziness, drowsiness, lightheadedness and the like were the side effects most frequently noted, particularly in elderly or debilitated patients.[3] Instances of hepatic dysfunction, paradoxical reactions (excitement) and hypotension are rare with Dalmane, and morning hang-over is relatively infrequent. In studies to date the effectiveness of Dalmane for recommended periods of use is maintained without need to increase dosage.

References: 1. Kales, A., *et al.:* "Effectiveness of Sleep Medications: All-Night EEG Studies of Hypnotic Drugs," in Proc. 7th Internat. Cong. Electroencephal. and Clin. Neurophysiol., San Diego, Calif., Sept. 13-19, 1969. **2.** Kales, A., *et al.:* "Psychophysiological and Biochemical Changes Following Use and Withdrawal of Hypnotics," in Kales, A. (ed): *Sleep: Physiology and Pathology,* Phila., Lippincott, 1969, p. 331. **3.** Data on file, Medical Department, Hoffmann-La Roche Inc.



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Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

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President's Letter

Physician Associate Program

The University of Minnesota Medical School is developing interesting innovations in its training of medical students. As you know, the preceptorship program initiated by the Minnesota Academy of General Practice has now become an approved elective. The student receives nine quarter credits for six weeks spent associated with a general practitioner in Minnesota. This program has proved popular with students and physicians alike.

Another interesting program that is being initiated is the Physician Associate Program or the Rural Medical Scholarship Program. In this program the student receives three quarters of basic science and five quarters of clinical work at the Medical School. Then he spends one year with a private physician, preferably a general practitioner or internist. The Medical School would provide a stipend for the first six months, and the physician would pay the student a similar amount for the last six months. In this way the physician would be asked to make a sacrifice in time and money to introduce these young men to practice in rural Minnesota.

I feel this is an excellent investment of a physician's time and money. These young men will have the training equivalent to a last quarter junior medical student when they join the physician. After spending some time with his physician instructor the student would be expected to perform many duties that would be of benefit to the physician.

In the past year, I have had the privilege of being associated with three senior medical students on preceptorship programs. All of these boys graduated in June and are now starting their internships. One of these students spent 3½ months with me instead of the usual six weeks. I was pleasantly surprised at how rapidly this young man was able to adjust to general practice. Patient acceptance was excellent and it was a real thrill to watch this young man's medical judgment mature so rapidly. After the first six weeks, Roy was a definite asset and help to me in treating patients. My only regret was that he was unable to spend an entire year with me.

The Physician Associate Program has a great deal of potential. I realize that the Private Physicians of Minnesota are being asked to make a sacrifice. However, to teach is to learn. I feel that I learned a great deal when I had a student helping me treat my patients. Besides the educational value, I have developed lasting friendships with outstanding young men.

I heartily endorse the Rural Medical Scholarship Program and encourage physicians of Minnesota to cooperate with our Medical School and, if possible, participate in this program.

Robert T. Kelly

President
Minnesota State Medical Association



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Cerebral Arterial Air Embolism

Selected Experimental Aspects

NORVAL M. SIMMS, M.D.,* DON M. LONG, M.D., Ph.D.,* and
LYLE A. FRENCH, M.D., Ph.D.*

In 1913 Brauer introduced the name "arterial air embolism" for the protean symptom-complex which followed entry of air into the arterial circulation.[4] Since that time the clinical aspects of cerebral air embolism have been well characterized.[10] Renewed interest in cerebral air embolism was associated with the extraordinary development of cardiopulmonary bypass techniques in the 1950s, as retention of air in the cardiovascular system represented a potential hazard to the patient.[5,16] Thus, interest in the experimental aspects of cerebral air embolism was fomented, and reports concerning air-induced changes in cerebrovascular permeability[14,16] and peripheral hemodynamic alterations[8,11] subsequently appeared in the medical literature. Our canine angiographic studies following vertebral artery air embolism revealed multifocal areas of vascular obstruction throughout the brain. Although many of the affected vessels re-established flow within an hour postembolism, it appeared that the diffuse nature of the process would produce dramatic alterations in intracranial blood flow dynamics. Continuing this interest, we undertook experiments concerning the effects of cerebral air embolism on regional cerebral blood flow and the acid-base status of sagittal venous blood and cerebrospinal fluid. The results of these studies are summarized in this report.

Materials and Methods

All animals were given atropine prior to induction of anesthesia with intravenous pentobarbital (30 mg/kg) and, subsequently, each animal was intubated with a cuffed tube and paralyzed with gallamine triethiodide (1 mg/kg). Using a Harvard Constant Volume Ventilator and room air enriched with oxygen, the minute respiratory volume was carefully controlled to maintain normocapnia. The femoral artery was cannulated for pressure measurements and arterial gas studies, and the femoral vein was used for administration of intravenous fluids and medications. The extraspinal portion of the right vertebral artery was cannulated at the base of the neck and a catheter was threaded toward the foramen magnum. Varying amounts of air, ranging from "massive" (1.0 ml/kg) to minimal (0.05 ml/kg), were injected into the intraspinal segment of the vertebral artery as a single bolus. Thirty-six healthy mongrel dogs were divided into three study groups as follows:

Group 1—Symptomatology

In this group of 14 dogs, the clinical appearance, peripheral hemodynamic status, and electrocardiographic changes were noted. The cisterna magna was punctured percutaneously for pressure measurements in seven animals, and the cerebrospinal fluid was intermittently aspirated for serial protein determinations in the remaining dogs.

Group 2—Blood Flow Rates

The second group, composed of eight dogs, was studied to assess alterations in regional cerebral blood flow. An animal was placed in either the supine or the left lateral recumbent position and a saline solution of xenon-133 (6 to 8 millicuries) was injected into the right vertebral artery to establish control flows. Following embolism with the predetermined amount of air, a second similar dose of radioxenon was administered. With the vertex of the skull in contact with an Anger gamma camera, control and post-embolic clearance curves were obtained from 16 to 22 regions of interest over

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Winning essay for the 1970 Minnesota Surgical Society.

both cerebral hemispheres. Regional flows were calculated on a computer according to the equation of Høedt-Rasmussen.[13]

Group 3—Acid-base Parameters

In the third group of 14 dogs, the superior sagittal sinus was cannulated through a midline posterior burr hole and a spinal needle was introduced percutaneously into the cisterna magna. With the animals in the left lateral recumbent position, oxygen (pO_2) and carbon dioxide (pCO_2) tensions and pH values of blood and cerebrospinal fluid were measured before embolism and four, 15, and 60 minutes following gaseous embolization.

Results

Group 1

The symptomatology resulting from cerebral air embolism is summarized in Table 1. The symptoms and signs evident in this group of animals are similar to those reported in other canine air embolism studies.[8,11] Bilateral mydriasis, loss of blink and corneal reflexes, and cardiac arrhythmias occurred within 30 seconds of gaseous embolization. The electrocardiographic tracings showed varying combinations of bradycardia, electrical alternans, bigeminy, and ST-T wave changes. These cardiac rhythm disturbances were most prominent during the first five minutes post embolism and occurred in six of the 14 animals sustaining macroscopic subarachnoid hemorrhage. Progressive post-embolic increases in cerebrospinal fluid protein levels occurred, even in the animals without gross subarachnoid hemorrhage. The present study corroborates the findings of De LaTorre et al.[8] who reported air-induced intracranial hypertension in the dog. With the larger amounts of air, cisternal pressure was not uncommonly augmented five-fold over that of baseline and was associated with bradycardia and systemic hypertension (Cushing reflex[6]). Similar responses of lesser magnitude were observed with smaller amounts of intravascular air.

TABLE 1
Effects of Cerebral Air Embolism

1. Bilateral mydriasis
2. Loss of blink and corneal reflexes
3. Subarachnoid hemorrhage with cardiac arrhythmias (large amounts of air)
4. Raised intracranial pressure with bradycardia and systemic hypertension (Cushing reflex)
5. Elevated cerebrospinal fluid protein levels
6.* Respiratory abnormalities
   a) apnea
   b) irregular ("ataxic") pattern
7.* Extensor hypertonia of extremities
8.* Opisthotonus

*Abnormalities noted in a separate group of animals which were not paralyzed.

Group 2

To simplify data analysis, blood flow was calculated for the composite of all regions counted. This value, the mean hemispheric flow, is termed the "total cerebral blood flow" (Table 2). Each animal experienced an acute enhancement in flow following cerebral air embolism. Since statistical analysis revealed that body position and amount of air did not have a significant effect on regional cerebral blood flow, the total cerebral blood flow data were pooled. Mean control flow was 28.3 ml/100 gm/min, whereas the post-embolic flow was 39.3 ml/100 gm/min. The mean difference, an increase of 11.0 ml/100 gm/min, is statistically highly significant ($p < 0.001$). Stated in other terms, the increase for the group averaged 39% above control levels.

TABLE 2
Effect of Air Embolism on Total Cerebral Blood Flow

Air Dosage (ml/kg)	Animal No.	CBF (ml/100 g/min) control	CBF (ml/100 g/min) post embolism
1.0	1†	26.3	37.3
	2*	37.6	48.0
0.5	3	35.9	40.9
	4	20.1	33.1
0.25	5	30.7	44.4
	6	24.8	42.9
0.05	7	27.9	38.1
	8	22.5	29.8

†Odd numbered animals: supine position.
*Even numbered animals: left lateral position.

Group 3

The pre-embolic pO_2, pCO_2, and pH values from each sampling site are presented in Table 3. Statistical analysis revealed no trend in magnitude of response at a given sampling site as a function of embolus size. Therefore, the data

for sampling sites at a given time post embolism were pooled. The serial mean changes from baseline status for each of the acid-base parameters are tabulated in Table 4. Examination of the data reveal that hyperoxia occurred in both sagittal venous blood and the cisternal cerebrospinal fluid following cerebral air embolism. The elevation of pO_2 values in these sampling sites was present four minutes post embolism and continued beyond the 60-minute sampling interval. During the period of venous and cerebrospinal fluid hyperoxia, the oxygen tension in arterial blood diminished. The hypoxemic response, present at four minutes following embolism, gradually returned to the pre-embolic level at 60 minutes. The pCO_2 rose modestly in all sampling sites following embolization, with the greatest mean rise (7.2 torr) occurring in femoral arterial blood at 15 minutes. The pH values declined as the pCO_2 levels rose, a relationship which could be predicted by consideration of the variables in the Henderson-Hasselbach equation.[7]

Discussions and Conclusions

Air introduced into arteries in various anatomical sites, including the brain, produces a biphasic hemodynamic response.[3,9] The initial phase is short-lived (two to three minutes) and is characterized by arteriolar blockade. This transient obstructive period is followed by prolonged vasodilatation. The vasodilator response to intra-arterial gas is attributed to local vascular trauma with loss of vasomotor tone.[9] Traumatic vasodilatation could be expected to alter cerebral autoregulation which normally maintains constancy of flow over a wide range of perfusion pressures; however, a normal head of pressure reaching a dilated vascular bed augments flow through that particular area. The early rise in systemic pressure occurring as a manifestation of the Cushing reflex, and the increased cardiac output which may follow,[15] would further promote flow through the cerebral capillaries. For these reasons, the protracted period of vasodilatation offers the most feasible explanation for the post-embolic enhancement in flow ("supernormal flow").

Hyperoxia of cerebral venous blood may occur principally in three settings.[17] The first possibility is that air may induce passage of arterial blood through previously dormant arteriovenous shunts into the venous side of the circulation. This mechanism is accorded minor importance because of the paucity of anatomical shunts in the canine brain.[12] Secondly,

TABLE 3
Mean Pre-Embolic (Control) Acid-Base Parameters: 14 Eupoxic Dogs

Sampling Site	pH (units)	pCO_2 (torr)	pO_2 (torr)
Femoral Artery	7.401 ±0.015*	31.4 ±1.9	161.6 ±9.8
Cisternal CSF	7.346 ±0.048	35.6 ±7.3	119.7 ±7.5
Sagittal Venous	7.343 ±0.039	43.9 ±3.8	60.5 ±9.4

*Represents mean ± 1 standard error.

TABLE 4
Absolute Mean Change in Acid-Base Parameters from Control (Pre-Embolic) Status

Parameter	Sampling Site	Time (Minutes) Post-Embolism 4	15	60
pO_2 (torr)	Cisternal CSF	15.9 ±4.5*	28.4 ±8.7	14.1 ±11.4
	Sagittal Venous	17.3 ±4.0	11.4 ±6.0	9.1 ±11.4
	Femoral Artery	—8.2 ±5.0†	—4.2 ±4.9	0.0 ± 6.5
pCO_2 (torr)	Cisternal CSF	—0.4 ±2.0	1.4 ±1.6	4.2 ±1.8
	Sagittal Venous	0.2 ±2.3	4.3 ±1.9	3.8 ±2.2
	Femoral Artery	4.6 ±1.7	7.2 ±1.9	2.0 ±1.4
pH (units)	Cisternal CSF	—0.003 ±0.009	—0.014 ±0.006	—0.034 ±0.013
	Sagittal Venous	0.002 ±0.006	—0.050 ±0.010	—0.058 ±0.013
	Femoral Artery	—0.011 ±0.006	—0.054 ±0.013	—0.058 ±0.013

*Represents mean ± 1 standard error.
†Negative values represent a decline from baseline status.

venous hyperoxia would eventuate if rapid flow through the cerebral capillaries delivers oxygen in excess of tissue need (physiologic shunting). The radioxenon clearance studies described in this report provide direct evidence that this absolute increase in flow is occurring. Thirdly, it is not unreasonable to suggest that the depression in aerobic metabolism resulting from ischemic hypoxia would diminish oxygen extraction from the cerebral capillaries, once again leading to an increase in the tension of this gas in the draining veins. Hyperoxia of the cerebrospinal fluid has been reported in primates following maneuvers which increase cerebral blood flow (CO_2 inhalation)[2,18]; therefore, the finding of post-embolic supernormal flow associated with elevations in cerebrospinal fluid oxygen tension was not totally unexpected. The hypoxemic response to cerebral air embolism may be due to the neural effects of intracranial hypertension on the vasculature of the lungs. This response of the pulmonary vessels, leading to venous admixture, may be due to the sympathetic discharge which occurs reflexly to raised intracranial pressure.[1] Carbon dioxide tensions rose in all sampling sites following cerebral air embolism. Embolic ischemic hypoxia, converting aerobic to anerobic metabolism, may be responsible for elevated cerebrospinal fluid and cerebral venous CO_2 tensions, whereas the hypercapnia may be related to the neurohemodynamic effects of intracranial hypertension.

Summary

Cerebral arterial air embolism produces a diverse array of pathophysiological changes including:

1. Dramatic neurological signs and symptoms due to multifocal vascular obstruction from air bubbles.
2. Raised intracranial pressure with bradycardia and systemic hypertension (Cushing reflex).
3. Subarachnoid hemorrhage with larger amounts of intravascular air.
4. Acute increases in regional cerebral blood flow attributed primarily to traumatic vasodilatation with physiologic shunting through the affected capillary beds.
5. Hyperoxia of cerebral venous blood and cisternal cerebrospinal fluid. The venous hyperoxic response is attributed to increased blood flow which not only delivers oxygen in excess of tissue need, but may also facilitate diffusion of the gas into the cerebrospinal fluid.
6. Hypoxemia occurs in face of cerebrospinal fluid and cerebral venous hyperoxia. Venous admixture in the pulmonary vascular bed occurring reflexly to raised intracranial pressure is advocated as the most likely explanation.
7. Elevations of pCO_2 with reciprocal diminutions in pH occur in arterial blood, cerebral venous blood, and cerebrospinal fluid. The effect in cerebral venous blood and cerebrospinal fluid is thought to be related to ischemic brain injury, whereas hypercapnia may be due to the neurohemodynamic sequelae of intracranial hypertension.

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8-18. May be secured from the author or the reprints.

Much smoking kills live men and cures dead swine.—George Prentice

Pulmonary Actinomycosis

Report of 18 Cases

THOMAS F. FOLEY, M.D.,* DAVID E. DINES, M.D.,†
CHARLES T. DOLAN, M.D.‡

Actinomycosis is a chronic suppurative infection characterized by a disregard of anatomic boundaries, although it classically involves cervicofacial, abdominal, and thoracic regions. Pulmonary actinomycosis is a rare disease, occurring most frequently in patients in the second through the fifth decades and more commonly in men (ratio 3:1).[1] Actinomycosis of the lung and pleura accounts for 15% of all forms of the infection.[2] No evidence has been accrued to indicate a concurrent underlying systemic disease, and most of the patients reported have been urban dwellers.[1]

When actinomycosis occurs in an adult male, particularly if the characteristic sulfur granules cannot be demonstrated in the sputum, differentiation of bronchogenic carcinoma is most important but may be impossible without thoracotomy.[3]

Clinical and Diagnostic Aspects

Clinical Findings

Eighteen patients with pulmonary actinomycosis were seen at the Mayo Clinic from 1946 through 1968. There were 13 males and five females, with a mean age of 47 years; the youngest was 13 years old and the oldest 73 years old. The duration of symptoms varied from three weeks to three years, and most patients complained of malaise, chills, low-grade fever, chronic productive cough, and pleuritic chest pain. Two patients had hemoptysis, and four had draining sinuses. Five of the 18 had poor dental hygiene. Nine patients were heavy smokers. One patient was a diabetic. One of

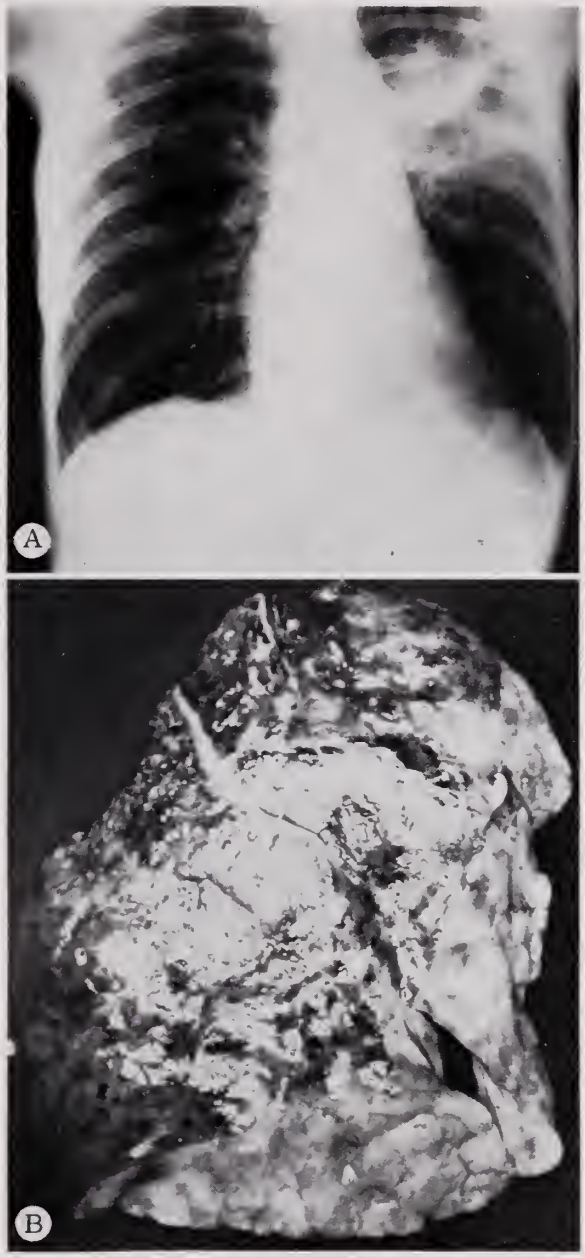


Fig. 1—(A) Infiltration in left upper lobe represents microabscesses of pulmonary actinomycosis. (B) Lung of patient with *A. israeli* demonstrates multiple abscesses in left upper lobe; patient died.

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‡Mayo Clinic and Mayo Foundation: Section of Microbiology.

the five was a young woman who had a left hemiparesis from an expanding intracranial lesion. Postmortem examination of this patient revealed a brain abscess containing *Actinomyces israeli* and multiple microabscesses of *A. israeli* in the left upper lobe of the lung (Figure 1); she had had an abscessed tooth pulled one month prior to her death.. One other patient with infected teeth had a chronic productive cough since a tonsillectomy three weeks prior to admission.

Physical examination of the 18 patients disclosed pleural fluid, pleural thickening, draining sinuses associated with chest wall masses, clubbing, and moist rales in the region of chronic pneumonitis. Two of the 18 patients had disseminated actinomycosis with multiple abscesses and draining sinuses as well as empyema; neither patient had underlying disease, although one was receiving steroids systemically.

Roentgenographic Findings

Nine patients had chest roentgenograms in which the findings were similar to those of primary bronchogenic carcinoma, with mass lesions and loss of volume (Figure 2). The roentgenograms of the other nine patients showed evidence of chronic pneumonitis and chronic empyema.



Fig. 2—Mass lesion resembles primary bronchogenic carcinoma.

Laboratory Findings

Routine laboratory studies were of no diagnostic help. Ten of the 18 patients were anemic; 12 had mild leukocytosis and a shift to the left; and 12 had elevation of the sedimentation rate.

Cultural Findings

In 16 of the 18 cases, sputum cultures were negative for fungi and *Mycobacterium tuberculosis*. The sputum cultures were positive for *Actinomyces* organisms in two of the 18 cases; anaerobic cultures were not done in the other 16 cases. Bronchoscopy was performed in five cases, and bronchial secretions were not studied anaerobically for *Actinomyces* organisms. The diagnosis was made at operation from culture of the tissue in 16 of the 18 cases. In one case, a culture from pleural fluid aspiration was positive. In another case (a patient with a brain abscess and multiple microabscesses in the left upper lobe of lung), the diagnosis was confirmed at postmortem examination. Other organisms cultured from the tissue include *Bacteroides* in one case, *Streptococcus pyogenes* organisms in one case, and saprophytic acid-fast bacilli in one case.

Surgery

Operation consisted of thoracotomy with open drainage and rib resection in nine, lobectomy in five, and pneumonectomy in two patients.

Pathologic Findings

The gross specimens consisted of lung lobes and segments of lobes resected at operation. The pleura showed varied degrees of fibrous thickening which microscopically was characterized by fibroblastic proliferation infiltrated with lymphocytes, plasma cells, histiocytes, and an occasional polymorphonuclear cell. Sulfur granules were not seen in the pleura available for study. The cut surfaces of the lung were gray-yellow to red with foci of necrosis (Figure 3). Frequently, bands of fibrous tissue could be seen between the foci of necrosis, which in advanced stages produced a multicystic fibrous chronic pneumonitis. Microscopically, the foci of

necrosis were infiltrated by polymorphonuclear cells surrounded by fibroblastic proliferation infiltrated with lymphocytes, plasma cells, histiocytes, and an occasional polymorphonuclear cell (Figure 4). The adjacent intact alveoli, peripheral to the fibrosis, were thickened and contained a fibrinous exudate with lymphocytes, plasma cells, and histiocytes. Occasional foci of vacuolated histiocytes were also noted. In eight of the cases, sulfur granules were identified predominantly in the areas of acute inflammation. Sections stained with hematoxylin and eosin did not delineate the filaments of *Actinomyces* (Figure 5-A). Gram-stained sections clearly demonstrated the thin (less than 1 μ in diameter) branching, gram-positive filaments, which were not acid-fast (Figure 5-B). Granulomas were not seen, but an occasional multinucleated histiocyte was identified. Histologic sections of the sinus tracts available for study were made up of dense fibrous tissue infiltrated with lymphocytes, plasma cells, and an occasional histiocyte.

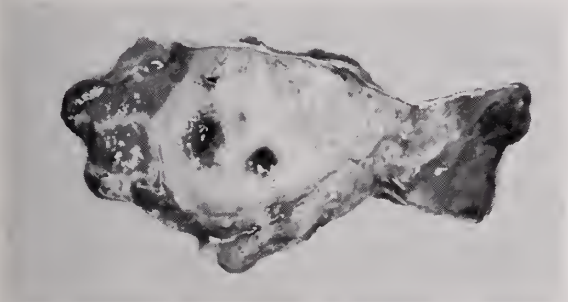


Fig. 3—Lung tissue with acute abscesses, chronic pneumonitis, and fibrosis characteristic of *Actinomyces* infection.

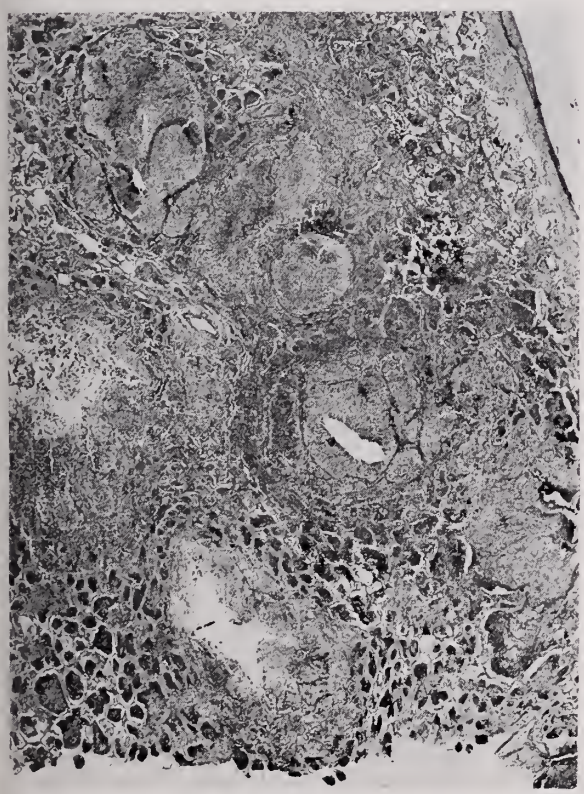


Fig. 4—Lung section with acute abscesses, acute and chronic inflammation, and early fibrosis. (Hematoxylin and eosin; ×10.)

The primary isolation of *Actinomyces* was made in thioglycolate broth, except for the last case in which the organism was isolated on brain-heart-infusion agar plates incubated anaerobically in 10% CO_2. Gram's stain of the broth showed branching, gram-positive filaments that were less than 1 μ in diameter and not acid-fast. Equal aliquots of a subculture of the thioglycollate broth suspension to agar plates of beef-heart infusion were made and incubated aerobically and anaerobically at 37

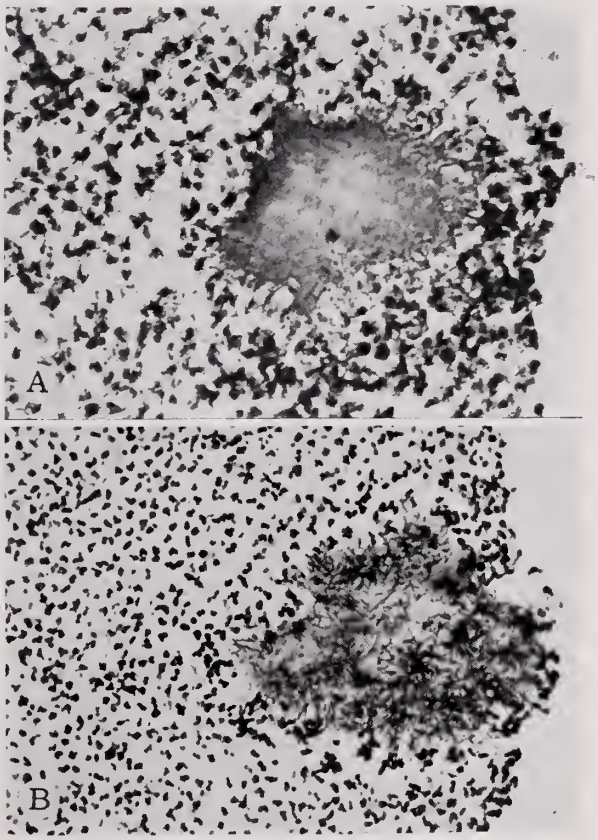


Fig. 5—(A) Sulfur granule in lung. (Hematoxylin and eosin; ×415.) (B) Same sulfur granule as in (A). (Gram's stain; ×250.) Note the gram-positive, branching, thin filaments not evident in section stained with hematoxylin and eosin.

C. Growth of *Actinomyces* organisms anaerobically, with little if any growth aerobically, was used to verify that the organism was microaerophilic. Species identification was based on colonial morphology and the type of growth in thioglycollate broth: *A. israeli* was characterized by rough colonies ("molar tooth") on beef-heart infusion agar and by granular growth in thioglycollate broth; and *A. bovis* was characterized by smooth colonies on beef-heart infusion agar and by diffuse growth in thioglycollate broth.

Treatment

Treatment, in addition to surgery, included 21 days of tetracycline for two patients and intramuscularly injected penicillin for 16; the duration of treatment in the penicillin-treated patients varied from four to 96 days.

Three patients were lost to follow-up; one patient with a brain abscess died; 14 patients were alive from one to 21 years after primary pulmonary infection.

Discussion

Mode of Entry

The *Actinomyces* organism enters the thorax one of several ways. The common mode is via the bronchial tree, either by inhalation of contaminated dust particles or by aspiration of contaminated matter from the enteric tract.[1,4] Emmons and associates[5] isolated, in pure culture, *A. israeli* from 10% of 100 pairs of tonsils. In 47% of these, they observed filaments that resembled *Actinomyces*. The second most common mode of entry is by direct extension from a source outside the thorax, usually the abdomen.[1,4] Less commonly, the organism may enter the thorax by perforation of the esophagus or via the bloodstream.[4,6]

Suppurative Character

The disease is suppurative and is characterized by extensive tissue destruction and abscess formation.[2,7] The pleural space is involved early, and chest-wall abscesses and draining sinuses frequently develop.[1,8] Thoracic actinomycosis tends to spread locally by direct extension.[9] Sepsis is unusual and tends to be associated with *A. israeli*.[1,8] Blood-borne metastasis occasionally can be found in other organs, including the brain, kidneys, and liver.[7,9] Empyema is common and was found in 20 of 85 patients in the series by Bates and Cruickshank.[1] Long-standing actinomycosis has been complicated by amyloidosis.[1,10]

Pulmonary Symptoms

The symptoms are those of any infectious process in the thorax. At some stage[1] a cough is almost always present, usually productive of purulent sputum, although it may be nonproductive initially.[10] Frequently the breath is foul-smelling. Hemoptysis of mild-to-moderate amounts is common, and occasionally gross pulmonary hemorrhage occurs.[11] Chest pain is common; frequently it is the presenting symptom;[1] it may be pleuritic. Usually patients have nonspecific symptoms, including fever, chills, sweats, loss of weight, and malaise.[11]

Physical Findings

Initially, physical findings may be absent. When present, however, they are usually those of pneumonitis, empyema, and draining sinuses. If sulfur granules are seen in exudate from a draining sinus, actinomycosis should be suspected.[12] The presence of sulfur granules is not diagnostic of *Actinomyces* infection; other organisms, including *Nocardia,* may produce such granules.[7,13]

Histopathology

The histologic demonstration in the sulfur granules of gram-positive, branching filaments less than 1 μ in diameter places the organism in the order Actinomycetales. The presence of these filaments eliminates the possibility of infection by deep fungi (the hyphae would be larger than 1 μ) or staphylococci (gram-positive cocci), which on occasion have produced sulfur granules. The differential diagnosis would then include *Mycobacterium, Actinomyces, Nocardia,* and *Streptomyces.* Infection by *Mycobacterium* can be eliminated if the isolated organism is anaerobic and not acid-fast. Also *Mycobacterium* infection presents different microscopic changes (granuloma) than does *Actinomyces* infection, and mycobacteria do not produce sulfur granules. *Streptomyces* organisms have not been implicated in lung disease and are aerobic, thus making the pres-

ence of these organisms unlikely. *Nocardia* is an aerobe, rarely produces sulfur granules, and is acid-fast.[14] The acid-fast quality of *Nocardia* must be studied with care, because older cultures and fixed tissue frequently do not show the acid-fast character of *Nocardia*. Decolorization with 1% sulfuric acid rather than acid-alcohol produces the most consistent results when the *Kinyoun* cold-staining acid-fast stain is used.[15] In 15 of the cases reported, cultural evidence of *Actinomyces* infection was obtained. In three cases, histologic evidence of infection was characterized by sulfur granules containing branching filaments that were gram-positive and less than 1 μ in diameter. *Nocardia* typically produces a diffuse distribution of filaments and rarely produces sulfur granules in one lung.[16]

Differential Diagnosis

The differentiation of *Actinomyces* based on colonial morphology and growth in thioglycollate broth is also not entirely reliable because there is some variation within species. More recent evidence indicates that biochemical tests are more reliable and that cell-wall analysis is the most definitive, but the later is impractical for most diagnostic laboratories.[17-19] The report by Blank and Georg[20] of using fluorescein-conjugated specific antisera offers promise of more rapid and accurate diagnosis for clinical laboratories.

When *Actinomyces* infection is suspected, the laboratory must be notified, because most clinical laboratories do not routinely look for anaerobic actinomycetes. Anaerobic cultures of bronchial washings and tissue biopsy material are the most likely aids in the diagnosis of pulmonary actinomycosis. However, in our cases in which a study was made for anaerobic *Actinomyces* organisms, sputum was positive in two. In our experience, anaerobic cultures of sputum rarely yield this organism even though it is a normal inhabitant of the oropharynx. The microbiology laboratory should undertake studies specific for anaerobes, because general and fungus cultures will not detect actinomycosis.

A roentgenogram of the chest may reveal increased bronchial markings, pneumonitis, pleural effusion, lung abscess, hilar mass lesion, peripheral mass lesion, or rib destruction.[8,10,21] The lower lobes of the lungs are involved more often than are the upper, and the disease is more often unilateral than bilateral.[9]

Frequently, patients with pulmonary actinomycosis are initially believed to have other diseases such as bacterial pneumonia, bacterial lung abscess, tuberculosis, or bronchogenic carcinoma.[21,22] Occasionally, a patient undergoes resection of a portion of one lung because bronchogenic carcinoma is suspected.[21] Nine of our patients had chest roentgenograms suggestive of primary bronchogenic carcinoma. In these patients, the correct diagnosis was made after the pathologic specimen was studied histologically and microbiologically. Usually, patients have a moderate leukocytosis and an elevated erythrocyte sedimentation rate. Frequently, microcytic anemia is present and may be severe.[1]

Treatment

If the patient is not treated, the course is chronic and progressive, usually terminating in death.[1,2] Therapy includes antibiotics and surgery. In the era before penicillin was available, vaccines, iodine, radiation treatment, thymol and sulfa drugs were used.[1]

Penicillin is the basic drug in the treatment of this disease.[1,23] *A. bovis* and *A. israeli* are usually sensitive to penicillin, and cures have been obtained with penicillin.[1,24] Therapy with large doses of penicillin for extended periods is probably the best treatment. Bates and Cruickshank[1] obtained good results with a regimen of 6,000,000 units of penicillin parenterally each day for 10 weeks, followed by 600,000 units orally each day for 10 more weeks. Of 42 patients so treated, 36 survived.

Tetracycline in a dose of 500 mg four times a day for 60 days has also been effective.[13]

Frequently, surgical drainage of pus accumulations (usually empyema) or resection of extensive lung lesions is required.[1,6,11,25] Relapse, after a course of therapy, is not infrequent; if relapse occurs[6,10] the patient should be given a second course of treatment. If treatment is persistent and aggressive, most patients can be cured.[1,11,12] Occasionally, a patient's condition will deteriorate rapidly in spite of aggressive therapy.[26]

Summary

Data on 18 patients with pulmonary actinomycosis reveal that five had poor dental hygiene. One patient had had an abscessed tooth pulled one month prior to her death; and another had a chronic productive cough since tonsillectomy three weeks prior to admission. Two of the 18 patients had disseminated actinomycosis, with empyema and draining sinuses as part of the disseminated disease. Nine patients had roentgenographic findings that resembled primary bronchogenic carcinoma, with mass lesions and loss of volume.

Aerobic sputum cultures and bronchoscopy were of little value in establishing the diagnosis; in only two of the 18 cases were sputum cultures studied anaerobically, and both were positive. In no case were anaerobic cultures requested of bronchial washings. The microbiology laboratory should look for these organisms, because general and fungus cultures will not detect actinomycosis. In 16 of the 18 cases, diagnosis was made at surgery. In one case, a culture from empyema fluid aspiration was positive. In another case (a patient with a brain abscess and multiple microabscesses in the left upper lobe), the diagnosis was confirmed at postmortem examination.

Microbiologic proof was confirmed in 16 cases and histologic proof in two cases. The pathologic specimen consistently showed chronic pneumonitis, multiple microabscesses, and fibrosis. Where the pleura was involved, there was chronic pleuritis.

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Suffer Senior Citizen

January 1, 1897. From a Doctor's Journal.

I have been out for consultation with Dr. Jabe Bidwell. This Dr. Bidwell has been practicing medicine in West Plattsburgh for many years. He has paralysis agitans terribly. He cannot really get into or out of a wagon alone. His hands tremble terribly. He only speaks in a whisper and people have to put their ear close to his lips to hear him. He can't put up his own medicines into powders or liquids, and yet he has a large practice. It seems strange that a doctor can hold his practice when in such a wretched physical condition. I hope when I get so debilitated my clients will stick by me.*

*David S. Kellogg, M.D.: A Doctor at All Hours, 1970. Edited by Allan Everest.

Myelomeningocele Birth Defect

Habilitation of the Child

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Approximately 100 children will be born each year in the state of Minnesota with a myelomeningocele defect. The physician who delivers the child is faced with the difficult task of telling the parents of the child's deformity and making decisions as to future evaluation and treatment. In the past, the infant born with myelomeningocele was viewed by physicians and society as having little or no chance for a productive and useful life; as a consequence, life-saving measures were withheld and the child was allowed to succumb. However, too often the untreated child continued to live for varying periods of time and developed progressive hydrocephalus, pressure ulcers, and renal damage. Subsequently these children either died slowly or spent the remainder of their lives totally dependent upon society.

Today there are new surgical procedures available which can improve the function of the defective organ systems of a child born with a myelomeningocele defect. The quality of pediatric and habilitative medicine offered these children has so improved that a re-evaluation of the previous pessimistic attitude is indicated.

The purpose of this paper is to outline a program of comprehensive long-term medical care which makes it possible for these children to achieve maximum function. We do not plan to discuss the genetics or embryology related to this deformity, as this information is readily available in the literature.[1,2,3,4,5,6,7]

Presenting Infant

Local Defect

The defect is usually obvious at birth; however, occasionally the only sign of spinal cord involvement may be a hairy patch over the spinal column, dribbling of urine or a clubfoot deformity. The skin over the protruding sac may be well epithelialized, although it is usually thin and tense. On transillumination, neural tissues may be visible.

Neurologic Alterations

If neural tissue is involved in the defect, then paresis and sensory alterations are usually present.

A child born with a thoracic defect almost always displays severe neurologic alteration: paresis of the abdominal and leg musculature and associated bladder and bowel dysfunction. In contrast, the child who presents with a cervical myelocele often has minimal neurologic alteration. Children born with a lumbar defect will have varying degrees of paresis in their lower extremities, nearly always associated with bowel and bladder dysfunction. When the lesion is confined to the sacral area, the triceps surae and gluteal muscle may be involved. If the lesion is below S2, then normal somatic muscular function is present, but diminished bowel and bladder control is usually observed.

Hydrocephalus

Hydrocephalus develops in 80% of children with a myelomeningocele defect[3] and usually becomes apparent clinically within the first month. In some individuals, hydrocephalus can progress without an apparent increase in cranial size,[3] but most often the two are closely correlated.

Orthopedic Defects

Orthopedic defects including clubfoot, subluxation or dislocation of the hips, and associated vertebral column defects are frequently seen at birth. Occasionally the child will also present with fracture of the femur secondary to a difficult delivery.

Management

Unless aggressive medical management is provided at birth, a great majority of these children will die. Lawrence[6] noted that 85% of the non-operated children died by one year of age. Sharrard[8-9] reported on a controlled study carried out to determine the value of immediate surgical correction of the myelomeningocele defect; he found that closure of the defect in the first 48 hours of life allowed the infant to

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maintain or improve his level of motor function, whereas the infant who did not receive surgical repair of the defect showed progressive deterioration of function. Rickham and Mawdsley[10] have found that 71 percent of the children who had surgical correction of their defect lived at least three years, whereas only 4 percent of the non-operated group lived.

In spite of the fact that infants tolerate surgery well within the first several days of life, there are authors[1,11] who advocate waiting six to 12 weeks before performing surgery so that the condition of the child will stabilize. Any delay in surgery increases the risk of rupturing the sac and of secondary meningitis. Matson[12] urges that if repair is to be done, it should be within the first 24 hours of life so as to reduce the chance of infection. In addition, proper positioning of the child with a bulging myelomeningocele sac is difficult and pressure sores develop easily. Moreover, lack of treatment of the defect is emotionally traumatic to the parents. For these reasons, immediate closure is advisable. Therefore, prompt referral to a medical center with experience in the evaluation and treatment of these children is essential.

Inpatient Care

At the University of Minnesota Hospitals any child referred for evaluation of a myelomeningocele defect is seen by the members of the Myelomeningocele Team for initial assessment. This includes a pediatrician, neurosurgeon, physiatrist, urologist and orthopedist.

Surgical Report of Cord Defect

The decision to repair the spinal cord defect and therefore commit the physicians and the parents to a long-term program is dependent upon many factors. A large open defect (rachischesis) that extends over some distance of the spine cannot be repaired. Also the intact sac that has a large base presents difficulty for early repair in the newborn because of the lack of adequate healthy skin for closure. This lesion should be treated conservatively until epithelialization of the sac and growth of the child makes surgical repair possible. The child who has other severe congenital defects, septicemia, or extreme hydrocephalus at birth is not considered an appropriate candidate for definitive surgical repair.

In most cases, the myelomeningocele defect is repaired, and it is advisable to do this within the first 24 hours after birth. The usual surgical approach is to excise the sac and retain all neural tissue. The dura is then closed or the paravertebral fascia is used to reinforce the area. There is no attempt to replace the bony defect.

Shunt for Hydrocephalus

Usually hydrocephalus is not definitively diagnosed until after the spinal cord defect has been repaired. If shunting is indicated, a ventriculoatrial shunt is most frequently utilized. At the present time, the Pudenz and Holter types of valve are used; these have greatly improved the treatment of hydrocephalus. Occasionally a shunt will be inserted to control the hydrocephalus before the spinal cord defect is repaired. This is usually done in those children who have a rapidly increasing hydrocephalus or a large sac which appears to be under excessive tension.

Correction of Orthopedic Defects

Attention must also be paid to nonsurgical complications that may be present. Immediate evaluation and treatment of hip subluxation is indicated. Often conservative treatment with proper positioning is all that is necessary. The use of plaster casts to maintain position is not contraindicated, although very careful application is necessary to prevent pressure ulcers from developing over the non-innervated skin areas. Likewise, early treatment of clubfoot can be initiated, and again proper casting is of great benefit.

Proper positioning and range of motion is begun as soon as possible. By instructing the parents how to carry out a home program and by closely observing the child in clinic, many deformities can be avoided.

Bladder Disfunctions

Urologic evaluation should be done in the newborn period. Often the first indication of bladder dysfunction is the infant's frequent dribbling of urine or inability to void with a good stream. However, even if the infant appears to have a normal voiding pattern, an urologic evaluation including cystometrogram, intravenous pyelogram, urine culture and re-

sidual urine are indicated.

Socioeconomic Evaluation

During the initial hospitalization, the baby's problems are discussed with the parents. It is important that they be made aware of the nature and severity of the multiple problems that they may encounter with the child and that it will require a long-term habilitative effort before he can function in society. They also need to have knowledge of what potential function the child might have. The information must be presented objectively and we must be able to make reasonable prognostications as to the child's future, provided he receives full benefit from the medical techniques that are offered.

In the isolated instance where it is our opinion that neurosurgical correction of the myelomeningocele defect or hydrocephalus will not be of benefit to the child or, in fact, might be detrimental, a home program is discussed with the family and the child is followed closely on an outpatient basis. If at any time there is reason to believe that this child would benefit from neurosurgical correction, then he is readmitted for the necessary procedures.

Before the child leaves the hospital, any necessary community resources should be contacted and included in the continued care of the child.

Office Care

The initial hospital treatment is only a first step in the care of these children. The multiple surgical procedures that were done have not cured the child; rather they have served primarily to control or reduce the deformity and complications. Treatment is continuous and never-ending; therefore, the Myelomeningocele Team should continue to follow the child and coordinate the treatment program.

The family physician must be actively involved in the child's care as he is the closest medical contact the family will have. Not only does he provide the medical care that these children need in areas not related to their congenital defect but, once aware of the unique medical problems that the child might develop, he can then initiate proper treatment or contact the appropriate specialist on the team.

Increase in intracranial pressure in infants usually results in a rapid increase in head size and a bulging fontanelle. In older children, a change in mental status, headaches, irritability or emesis might be the only sign of altered ventricular pressure.

Otitis

Ear infection poses a special problem for the child with hydrocephalus as this can lead to ventricular obstruction. Therefore, appropriate antibiotic treatment must be initiated in any child with hydrocephalus and otitis media. A common cause of shunt dysfunction is dislocation of the atrial end of the catheter. A chest x-ray will reveal proper catheter location and, if indicated, replacement of the catheter will relieve the problem.

Urinary Tract

Urinary tract infection and progressive renal deterioration may occur without clinical manifestations; therefore a urine culture and voiding cystometrogram are indicated every three months. Ideally, the urologist on the Myelomeningocele Team should evaluate the studies.

Impaired Sensation

The child with lack of sensation is obviously susceptible to pressure ulcers and skin abrasion. The family must be taught proper preventive-care methods. If a pressure ulcer does develop, prompt treatment can often avoid the severe complications that too often ensue. Even the smallest pressure ulcer must be treated vigorously. This should include complete removal of all irritants or pressure over the involved area, and the wound should be kept clean and dry.

Osteoporosis is a common finding in the bones of a paralyzed limb. The child who does not have sensation and is not aware of limb position is most likely to fracture an osteoporotic long bone. Too often these fractures go unnoticed; this can result in improper healing.

The Myelomeningocele Clinic

The child is reevaluated at three-to-six-month intervals by the same group of physicians who saw him during the initial hospitalization. In addition, a social worker and a psychologist are available for consultation.

Having the child seen on the same clinic visit by each of the physicians involved with his care accomplishes two purposes. It greatly reduces the number of clinic visits and, secondly, gives the physicians involved a chance to dis-

cuss the child and plan together for future care.

After the child has been seen by the various members of the team, recommendations are discussed with the family and a detailed report is sent to the family physician. It has been our experience that the family physicians desire such a clinic and are better able to provide continued medical care if they are kept informed of our recommendations.

Functional Capacity

Our primary goal is to provide optimal medical care so that these children may function in society. There are five functional goals that we should strive for. (1) Good renal function must be maintained; (2) an adequate method of urine and feces control must be established; (3) the child should have an independent method of locomotion; (4) he must be able to provide his own self care and become self supporting; (5) he should be socially acceptable.

It is our belief that these goals are attainable in most of the children by the time they are ready for grade school. To achieve these goals usually requires periodic hospitalization, multiple surgical procedures, and hours of habilitation therapy.

Bladder and Bowel

As mentioned earlier, one of the most serious concerns is renal damage. If it becomes apparent that the child will have persistent bladder dysfunction, or if there is evidence of renal damage, then surgical intervention will be necessary. In most instances, an ileac diversion is the procedure of choice since it helps prevent deterioration of renal function and allows the best social rehabilitation. Experimental studies suggest that in the future electrical bladder stimulation combined with an externally controlled implantable continence device may provide volitional control of micturation for many of these children. Bowel training is possible in almost all of the children and is usually achieved by age three years.

Locomotion

The early treatment of a hip dislocation or other orthopedic deformities is necessary to insure the child's chance to walk. Likewise, prevention of contractures (Figure 1) allows the child to utilize his available muscle function



Fig. 1—Two-and-a-half-year-old girl, with a repaired lumbar myelomeningocele, shown receiving prolonged hip flexor stretch.



Fig. 2—Two boys, with repaired lumbar defects and both successfully shunted for hydrocephalus, shown ambulating with assistive devices.

to its greatest advantage. When indicated, muscle transfers and tenotomies are done to improve limb function. The diagnosis and treatment of scoliosis and kyphosis must be aggressive, as these deformities are progressive and cause severe disability. Spinal fusion is often the only way to control these deformities.

As the child matures, emphasis on the means of locomotion increases. Initially we stress upper extremity strengthening and improved trunk and body balance. The age at which the child begins to ambulate is variable and depends upon the severity of the defect. The child with complete paraplegia can usually be ambulating with crutches and long leg braces by five years of age (Fig. 2). Children with less involvement are able to walk by two or three years.

Intellectual Training

Intellectual function should be evaluated no later than the summer before entering school. The Stanford-Binet or WISC tests are useful in assessing general intelligence; however, visual and auditory perception, hand-eye coordination, language and comprehension should be evaluated to determine the child's functional capability. Specific areas of impairment should be recognized early so that other intellectual skills may be developed and specific training provided.

Preliminary Clinical Results

There are 34 children presently involved in this evaluation. Most of them have been followed at the University Hospitals from either the newborn period or since the first year of life. The oldest child is eight and one-half years of age. There are 10 children who are at least five years of age. They display varying degrees of spinal cord involvement and the level of their defect varies. The following data pertains to these 10 children.

Bladder dysfunction is present in eight of the 10 and seven have required an ileac diversion. At the present time, each child with a diversion appears to have good renal function. All of the ten have been placed on successful bowel training programs and seldom have fecal soiling.

Nine of the 10 children are able to ambulate and the tenth child is presently walking in the parallel bars. While three of the children walk only in their home or at school, for the remaining six functional ambulation has been achieved. Eight of the 10 children do require varying degrees of lower extremity bracing.

Eight of the children have required shunting procedures for control of hydrocephalus. None display any evidence of increased intracranial pressure.

Nine are attending regular public school and the tenth child is in a class at a public school for physically disabled children. Six children are in kindergarten and five are expected to start first grade next year. The four who are in grade school are all reading at an average or above average level.

This series of patients is too small to accurately assess the full benefit of comprehensive medical care. It is also apparent that our study population is not an accurate cross-section of the children with myelomeningocele, as those who have died, those transferred to other institutions for care, or those lost to follow-up are not included. However, it is evident that many with myelomeningocele defect will eventually function independently in society.

Summary

Most children born with a myelomeningocele defect have paresis of their lower extremity muscles, hydrocephalus and bladder dysfunction. In the past, our degree of medical knowledge was insufficient to provide adequate treatment for this disability. Today we have the medical knowledge required to successfully treat many of the children born with this defect.

Because there is multiple system involvement, the child requires treatment from many medical specialists. However, the multi-discipline treatment approach fails if there is not coordination of the team and if good communication with the family physician is not maintained.

For these reasons, a coordinated multi-discipline clinic has been established at the University of Minnesota Hospitals for the treatment of children with a myelomeningocele defect. Initial evidence would indicate that a majority

come functional in society. If this remains true, then myelomeningocele, while still a most serious congenital defect, will no longer be considered a hopeless one.

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Abstract

Intravenous Catheter Embolization To The Pulmonary Artery

Two cases of polyethylene catheter embolization from peripheral sites to pulmonary artery are reported. The literature is reviewed. In the case presented, a right thoracotomy was carried out and the catheter was removed. The patient tolerated this surgery satisfactorily and had no important sequelae. The author suggests the following criteria to reduce the complications associated with the use of indwelling polyethylene catheters:

1. Catheters should be used only in critically ill patients and those requiring prolonged intravenous therapy.
2. The catheters should be radiopaque.
3. The catheters should be measured and their recorded length should be noted prior to insertion.
4. One should protect the plastic tubing from the shearing force of the needle.
5. Avoid flexion areas such as the anticubital fossa.
6. Secure the plastic polyethylene catheter to the skin.
7. Polyethylene indwelling catheters should be used only with extreme caution in restless patients and the adjacent joint should be splinted in such a way that the catheter cannot be displaced.
8. Critical aseptic technique should be maintained at all times.

The authors suggest removal of all embolized catheters regardless of their position.

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Minneapolis, Minnesota

Louis C. Bernhardt, M.D., Gene P. Wegner, M.D., John T. Mendenhall, M.D. Chest 57: 4: 329-332, April 1970.

Some women blush when they are kissed; some call for the police; some bite. But the worst are those who laugh.—Author unidentified

Tuberculosis

A Misunderstood Disease

J. A. MYERS, M.D. AND JOHN F. BRIGGS, M.D.

BEFORE ANY FORM of treatment is administered for tuberculosis, accurate diagnosis is essential and accurate diagnosis is dependent on knowledge of pathogenesis of the disease.

Early Pathogenesis

When tubercle bacilli enter the body by any portal, they are promptly phagocytosed by neutrophils which focalize them in small capillaries in various parts of the body—more in the lungs than in any other organ. At these points of focalization, the reaction of the tissues is only that of a foreign body. They are surrounded first by neutrophils, then by monocytes and later by columns of lymphocytes. Fibrous tissue is then deposited around the outer surface of tubercles, and caseous material containing tubercle bacilli accumulates in the center.

In the early stage of tubercle development, some bacilli are carried by lymphatics to the regional lymph nodes where tubercles are also produced. An original pulmonary focus and the foci in the lymph nodes constitute a primary tuberculosis complex. Within three to seven weeks after tubercle bacilli are focalized, their protein has sensitized the tissues of the host. After this hypersensitivity (allergy) to tuberculoprotein is established, this protein is a violent poison to them, hence, they react specifically when it comes in contact with them. Allergy results in increase of the central necrosis and increase of the fibrosis at the periphery of nodular tubercles.

Krause observed that the fibrous wall of nodular tubercle becomes completely "tight." *"Thoroughly avascular itself,* tubercle can communicate with the surrounding tissue only through the intermediation of tissue lymph."

Diagnosis

The diagnosis of primary tuberculosis is first possible within three to seven weeks after focalization of tubercle bacilli by a reaction to tuberculin when the host's tissue becomes hypersensitive to tuberculoprotein. At this time, usually 5 units (5 TU) of purified protein derivative (PPD) or a corresponding amount of original (old) tuberculin (OT) is adequate to result in a reaction to the tuberculin test. This dose of tuberculin is sufficient to identify the presence of lesions in persons relatively recently infected, including school children, college and university students, military recruits, and older persons, who become initially infected later in life. However, much larger doses of tuberculin may be necessary for persons of any age who have acute, rapidly progressive disease such as meningitis and miliary dissemination. This also applies to persons with long standing infections particularly the elderly.

Lesions of primary tuberculosis complexes cause no symptoms before the body tissues become hypersensitive to tuberculoprotein. At that time, however, mild symptoms including malaise and fever may appear in some cases but are of short duration. If symptoms appear they are so similar to those of influenza that even if a physician is consulted, tuberculosis is not diagnosed unless the tuberculin test is administered. There is no important physical sign and in 95 percent or more, roentgenography reveals no abnormality. In 5 percent or less, a primary pulmonary infiltrate may be of sufficient size, density and location to cast a visible shadow. However, without causing significant illness, the lesion usually slowly resolves.

Among persons of any age who develop primary tuberculosis, it has been estimated that in 95 percent the bacilli remain locked up in avascular capsules. In approximately one fourth of the hosts, calcium is deposited later within the capsules in sufficient amounts to cast visible

shadows on roentgenograms. In the vast majority of cases, no further evidence of tuberculosis other than hypersensitivity to tuberculin appears during the remainder of the lifetime of the host.

Primary tuberculous lesions are nearly always brought under control by the natural defense mechanism of the human body. In fact, on the basis of spot tuberculin testing, it has been estimated that approximately one half of the people of the world now have primary tuberculosis, very few of whom are aware of its presence.

If antituberculosis drugs are employed for primary tuberculosis, they should be administered promptly after tuberculin conversion occurs. Two of the major ones should be prescribed, preferably isoniazid and para aminosalicylic acid. If for any reason, one of these drugs does not prove satisfactory, streptomycin should be substituted.

Among those persons for whom drug administration is started within three months after tuberculin conversion occurs, 100 percent have been found to revert to nonreactors to tuberculin within a year or less. A considerable percentage of those known to have had tuberculin conversion within six to 12 months before drug administration is begun have tuberculin reversion within a year. However, among those whose tuberculin conversion occurs more than a year before drug administration begins are not likely to revert. This probably is because of the avascular state of the primary lesions making it impossible for drugs to contact their tubercle bacilli. There is no immediate way to determine whether reversion of the tuberculin reaction in those with infection occurring one year or less after infection occurs indicates that all tubercle bacilli have died or that they have only been suppressed to such a low level that they are not liberating tuberculoprotein in sufficient amount to maintain allergy at a high enough level to be detectable by the tuberculin test.

Therefore, *knowledge of the pathogenesis of tuberculosis is essential to understand treatment of this disease.* Without this knowledge, methods may be adopted which could not possibly produce the alleged results. Knowing that lesions of primary complexes become densely walled off and are avascular within a year or less, means that if drugs are to reach the tubercle bacilli, they must be administered before primary lesions lose their vascularity.

Reinfection (Endogenous) Tuberculosis

Although primary tuberculosis is exceedingly benign and causes no significant tissue destruction, it sets the stage for the development of the destructive clinical type of disease. In an estimated 5 percent of persons who develop primary tuberculosis, nature erodes or absorbs parts of walls of tubercles so as to allow tubercle bacilli to "leak out" without resulting in change of the primary lesion. Thus the primary lesion does not recrudesce (break out again: renew activity). It only liberates caseous material containing tubercle bacilli. Wherever these tubercle bacilli lodge, the allergic tissues react specifically to their protein, resulting in inflammation. If this endogenous reinfection occurs in a serous space, fluid accumulates; if in the lymph or blood stream, miliary dissemination may occur. If in large numbers in bronchial ramifications and aspirated peripherally, tuberculous pneumonia, or if in small numbers, chronic pulmonary lesions may develop. These endogenous reinfections have a strong propensity to progress. They result in most of the destructive clinical disease that occurs in the human body.

Some chronic pulmonary lesions may be brought promptly under permanent control by the body's defense mechanism. Others may progress continuously or intermittently to long-term illness and some to fatal termination.

Diagnosis

There are only two specific findings to justify diagnosis—namely reaction to tuberculin and recovery of tubercle bacilli. When first detected, the extent of disease may range from a single lesion so located, barely large enough and with sufficient consistency to be demonstrable on roentgenogram to extensive cavitary lesions in one or both lungs. More than a third of a century ago, it was demonstrated that chronic pulmonary tuberculosis can be detected two or three years before it becomes communicable or causes illness. The method consists of making roentgenograms periodically of the chests of youths and adults whose only evidence is a tuberculin reaction.

Management

The patient found to have communicable pulmonary tuberculosis should be hospitalized promptly in a General Hospital or a sanatorium

where facilities are available for the practice of communicable disease technic. This technic is exceedingly important for the protection of all uninfected persons, including students and graduates of nursing and medicine. Communicable disease technic includes attempts to prevent particulate material of all sizes from being ejected into the environment during the patient's coughing, sneezing, and talking. This is accomplished in part by having him cover the mouth during these acts with gauze, paper napkin, or mask. During sleeping periods, masks may become displaced and particles of various sizes may be ejected into the atmosphere. The larger particles are deposited in numerous places, including floors, furniture, bedding, food, dishes, clothing, face, hands and hair of human associates from which they may reach the mouths of personnel and visitors. Microscopic particles may float in the air for considerable time and some may enter the nares and the mouths of people before settling.

Because some particles of various sizes containing tubercle bacilli are released in the patient's environment, persons who enter the patient's room should be protected by caps, masks, and gowns with thorough washing of the hands and arms on leaving.

In addition to the well known hospital and sanatorium procedures, antituberculosis drugs should be administered as soon as possible after the diagnosis is established. The three major drugs employed in the chemotherapy of tuberculosis are streptomycin, aminosalicylic acid and isoniazid. Other drugs later produced which have recently acquired high rating and may be substituted for one or more of the three usual drugs are ethembutal and rifadin (rifampin). While there are several other drugs classified as second rate, some of them are useful when one or more first-class drugs are not effective for such reasons as acquired resistance of tubercle bacilli or sensitivity of the host's tissues to them.

If cavities do not close or lesions do not respond to antituberculosis drugs, resectional surgery may be performed on suitable cases. Such persons should be retained in institutions for a considerable period of time after tubercle bacilli are no longer recovered from sputum or bronchial secretions obtained by bronchial lavage and gastric washings. After discharge from the hospital, the patient should continue on chemotherapy 18 or more months depending on circumstances.

Patients found to have minimal tuberculous pulmonary lesions proved to be tuberculous are best hospitalized for at least a few months while the anti-tuberculosis drug schedule is being regulated and especially for a period of information concerning this lifetime disease. After discharge, drugs should be continued for 12 months or longer depending upon individual cases.

The Physician as he Sees Himself

I was called not long since to an ingenious gentleman who had recovered from a fever, but a few days before he had employed another physician, who blooded and purged him soundly, and forbade him the use of flesh. When I came I found him up, and heard him talking sensibly. I asked why I was sent for, to which one of his friends replied with a wink, Wait and you'll see. Accordingly, sitting down and entering into discourse with the patient, I perceived his under lip was thrust outwards, and in frequent motion, as happens to peevish children, who pout before they cry, which was succeeded by the most violent fit of crying, with deep convulsive sobs. I conceived this was occasioned partly by his long illness, partly by the previous evacuations, and partly by emptiness; *I therefore ordered him a roast chicken and a pint of canary.**

*Thomas Sydenham (1624-1689) as quoted in A. C. Corcoran, M.D., A Mirror up to Medicine, 1961.

There are men so conservative they believe nothing should be done for the first time.

Stevens-Johnson Syndrome

Severe erythema multiforme-like eruption of the skin and orificial mucous membranes, fever, and constitutional symptoms characterize this syndrome. Although reported for many years under various descriptive terms, it has become best known as Stevens-Johnson syndrome (1922). It usually occurs in young adult males, rarely in infants, children, or adults over 50 years of age.

Onset is preceded by prodromal symptoms of general malaise, headache, chills, and fever. An acute respiratory infection is often present. Erythematous, vesicular, and bullous lesions appear on the buccal mucosa, tongue, lips, face, eyes, and genitalia, sometimes accompanied by ulceration and bleeding. Within a few days the hands and feet and other parts of the body may be similarly affected. Mucous membrane involvement is seen in varying degrees of conjunctivitis, rhinitis, balantitis, and urethritis. A complicating corneal or iris involvement, hypopyon, or chemosis frequently accompanies the conjunctivitis.

The etiology is unknown. A virus of allergic origin has been suspected. The syndromes of Behcet and Reiter together with this disorder are thought to be variants of erythema multiforme exudativum (Robinson and McCrumb). At times the syndrome is difficult to differentiate from acute pemphigus except for the latter's grave prognosis.

The severe symptoms persist for approximately ten days The vesicular lesions crust and heal in three to six weeks, but in some cases recurrences are common. Although recovery is the rule, severe cases may be fatal in spite of treatment. The eye lesions are often grave, resulting in partial or total blindness. Steroid therapy is usually not satisfactory, but occasionally it has shown dramatic results. Antibiotic and adjunctive antihistamine therapy have been effectual in some cases.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

It's The Law

Physician Liable For Death Due To Post-Surgical Embolism

The patient sustained a fracture dislocation of the ankle which required open reduction and pin fixation. Approximately eight days after surgery, the patient suffered shortness of breath, right chest pain and elevated right diaphragm. On EKG a pulmonary embolus was suspected. Anticoagulants were not used. The patient was discharged from the hospital and subsequently suffered a massive fatal pulmonary embolus. He was awarded a $500,000 verdict.

Why do doctors so often make mistakes? Because they are not sufficiently individual in their diagnosis or their treatment. They class a sick man under some given department of their nosology, whereas every invalid is really a special case, a unique example. How is it possible that so coarse a method of sifting should produce judicious therapeutics? . . . The principal grievance which I have against the doctors is that they neglect the real problem, which is to seize the unity of the individual who claims their care.*

*Amiel, H. F. in Richard MaGraw: Ferment in Medicine, 1966.

Mycoplasma Pneumonia Infection

Associated with Stevens-Johnson Syndrome*

JAMES J. HOUSER, LCDR, MC, USN, AND NEIL R. HOFFMAN, LCDR*, MC, USNR

MYCOPLASMA PNEUMONIAE is a common cause of pneumonia in young adults.[1] The illness is characterized by fever, pharyngitis, cough, and a lower respiratory infection with pulmonary infiltrates, usually in the lower lobes.[2]

The association of erythema multiforme and Stevens-Johnson syndrome, with Mycoplasma pneumoniae infections, has been described recently.[3,4,5] To date, 35 cases have been reported stressing the early use of corticosteroids as part of the treatment program.[3-9]

This report presents two additional cases of Stevens-Johnson syndrome in association with Mycoplasma pneumoniae infection. Both patients were extremely ill. They experienced generalized malaise, complained of difficulty in swallowing, and had vesicular lesions involving the entire pharynx. Both patients recovered rapidly with supportive treatment and antibiotic therapy. Concurrent corticosteroid administration was not employed.

Case Reports

Case 1

A 22-year-old man was in good health until July, 1969, when he noted malaise, rhinorrhea and generalized myalgia, followed in 48 hours by nausea, anorexia, and a cough, productive of thick, greenish sputum. Subsequently, chills, fever to 101°F (oral), and occasional vomiting were noted. He was admitted to the Naval Hospital, Oakland, California, seven days after onset of the initial symptoms.

Physical examination revealed an alert, but toxic-appearing white man. Nasal membranes were reddened and dry, and pharyngeal mucosa and soft palate contained diffuse punctate hemorrhages. Decreased breath sounds with fine end-inspiratory rales were noted in the right upper lobe posteriorly. There were no vesicles or exanthem. Chest x-ray revealed a soft, fluffy infiltrate in the right upper lobe. White blood cell count was 6400 per cu. mm. Gram stain and culture of sputum showed no abnormal bacteria. Fluorescent antibody staining of sputum was negative for M. tuberculosis. Coccidioidin, histoplasmin and tuberculin (purified protein derivative, both intermediate and second strength) skin tests were negative at 48 and 72 hours. VDRL was non-reactive. Cold agglutinins titer was positive in 1:1024 dilution. Sputum cultured on 0.002% methylene blue pleuropneumonia-like organism agar grew Mycoplasma pneumoniae.

On the second hospital day he became nauseated, temperature was 102°F, and he complained of pain with swallowing. Pharyngitis and cervical lymphadenopathy were more prominent. The next day he developed severe stomatitis and a generalized confluent erythematous macular eruption. Some lesions were urticarial. Vague myalgias, arthralgias and photophobia were present. Funduscopic evaluation, including slit lamp examination, was normal. The conjunctiva were not affected. Stevens-Johnson syndrome was diagnosed on the basis of the symmetrical erythematous, urticarial, and bullous lesions of the face, pharynx, soft palate and trunk. There was no peripheral spread of the lesion, and no target or annular lesions were seen.

Treatment consisted of intravenous fluids, analgesics, and cold compresses to the affected skin areas. Saline lavages were beneficial for the pharyngitis. Tetracycline, 0.5 gm every six hours, was given by mouth. Within 48 hours he was afebrile and the exanthem faded. Two days later the only manifestations that remained were the resolving stomatitis and pharyngitis. By the seventh day the chest x-ray cleared.

Case 2

A 21-year-old man was well until early December, 1969, when he noted easy fatigue, chills, and sore throat, followed several days later by generalized myalgia. These symptoms resolved slightly but persisted for the next 12 days. He then noted anorexia and a reddened, non-pruritic rash on the inner aspect of the right upper arm. The next day the rash had spread to include the entire trunk, neck, proximal portions of all extremities, face and palms of the hands. At this time a low-grade fever, 100°F (oral), developed, and the sore throat worsened. He was admitted to the Naval Hospital, Oakland, California, for further evaluation.

Physical examination on admission revealed a mildly dehydrated and toxic-appearing man with a fever of 100.4°F. A confluent, maculopapular rash involved the arms, trunk, neck, face and palms. The soft palate, uvula, pharynx, and peri-tonsillar areas demonstrated punctate hemorrhages, and Stevens-Johnson syndrome was diagnosed. There was no involvement of the con-

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The opinions or assertions contained herein are those of the authors and are not to be construed as official or necessarily reflecting the views of the Medical Department of the Navy or the Naval Service at large.

junctiva or penis. No adenopathy was present. The remainder of the physical examination was normal.

Chest x-ray revealed a soft infiltrate in the right upper lobe. White blood cell count was 13,700 per cu. mm. with 90% granulocytes. Gram stain and routine culture of sputum showed normal flora. Sputum grown on 0.002% methylene blue pleuropneumonia-like organism agar produced Mycoplasma pneumoniae. Histoplasmin, coccidioidin and tuberculin (purified protein derivative intermediate strength) skin tests were negative at 48 and 72 hours.

On the second hospital day, tetracycline, 0.5 mg by mouth every six hours, was given. Within 48 hours he was afebrile, and by the fifth day was totally asymptomatic. Tetracycline therapy was continued until the tenth day when all lesions of skin and mucous membranes had disappeared. The chest x-ray reverted to normal two weeks after admission.

Comment

Stevens-Johnson syndrome has been associated with a variety of conditions, including systemic infections, herpes simplex, drug and food intolerance, pregnancy, occult tumors, infections due to varied viral and bacterial agents, and parasitic infections.[2,7] The syndrome has been described as a severe variant of erythema multiforme, usually occurring in a younger age group, and associated with a high fever, headache, fulminant stomatitis, conjunctivitis, arthritis, urethritis, and balanitis.[2] Neither of our patients had conjunctivitis, arthritis, urethritis or balanitis, although both had severe stomatitis with a high fever. Neither had received or taken any medications prior to the appearance of the rash.

The relationship between Mycoplasma pneumoniae and Stevens-Johnson syndrome was first reported in 1964 by Ludlam et al.[6] who demonstrated elevated complement fixing antibody titers to the organism. Ström[9] in 1965 reported rising titers of cold agglutinins in patients with Stevens-Johnson syndrome. Foy et al.[3] in 1966 isolated Mycoplasma pneumoniae from throat swabs of a patient with Stevens-Johnson syndrome,* as did Sieber et al.[4] and Katz et al.[7] in 1967. Lyell et al.[8] in 1967 isolated Mycoplasma pneumoniae from blister fluid of two patients and from throat swabs of three patients with erythema multiforme. Cannell et al.[5] in 1967 isolated Mycoplasma pneumoniae from sputum samples in a patient with Stevens-Johnson syndrome and pneumonia. With these reports in mind, we looked among our patients with Stevens-Johnson syndrome for possible Mycoplasma pneumoniae infection, and sputum samples of suspect patients were cultured on specific agar. The relationship between Mycoplasma infections and erythema multiforme syndromes may be more frequent than is reported, and should be looked for more often.

Recommendations for treatment of Stevens-Johnson syndrome have uniformly included intensive systemic corticosteroid therapy. Recent case reports have described the administration of corticosteroid medications in high dosage with good results.[3,4,5,7] However, because of the absence of ocular findings, and the possible deleterious effect of oral corticosteroids, treatment was limited to tetracycline antibiotic, and to symptomatic therapy, with cold compresses to the skin, and saline lavage of the pharynx and mouth. The rapid recovery of our extremely toxic-appearing patients, suggests that this syndrome will regress with antibiotic and supportive treatment of the primary disorder.

Conclusions

Mycoplasma pneumoniae is a common infection in young adults.[2] In the past five years, 35 cases[3-9] have been reported in which infection with this organism was accompanied by Stevens-Johnson syndrome, and two additional cases are reported. The possibility of an association between these diseases is raised and perhaps is more common than previously reported. The cases presented were of toxic and severely-ill patients whose symptoms and signs responded to antibiotic treatment without corticosteroid therapy.

See page 608.

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The fate of nations depends upon how they are fed.—Brillat-Savarin.

Chronic Milk-Alkali Syndrome and Salt-Losing Nephropathy*

AZAM ANSARI, M.D.* AND J. A. VENNES, M.D.*

In 1944 THORN and associates[1] described two patients in whom renal failure simulated adrenocortical insufficiency, who also had polyuria and symptoms of salt deficiency associated with renal rather than adrenal disease, and in whom adrenal function tests were normal with demonstrably moderate to severe renal insufficiency. Both patients improved with sodium repletion therapy. Thorn proposed the term "salt-losing nephritis" for such patients with chronic renal insufficiency who present evident signs and symptoms of sodium depletion.

The existence of a clinical syndrome of "salt-losing renal disease" has since been amply confirmed. About 37 cases have been described (Table). "Salt-losing nephritis" is probably an inappropriate term because the affix 'itis' implies inflammation, which is not the pathologic feature. "Salt-losing nephropathy" is more accurate.

In 1949 Burnett and his associates[2] described another clinical syndrome with renal insufficiency in six patients after prolonged intake of milk and alkali for relief of peptic ulcer symptoms. The syndrome is characterized by hypercalcemia without hypercalciuria or hypophosphatemia, mild alkalosis, normal serum alkaline phosphatase and renal insufficiency. Calcinosis may be manifested by either band keratopathy or nephrocalcinosis. Improvement in clinical and chemical abnormalities may become evident on the withdrawal of milk and absorbable alkali.

During the past 20 years about 50 cases of chronic milk-alkali syndrome have been described. Acute and subacute milk-alkali syndrome are excluded from consideration in this report.

"Salt-losing nephritis" simulating adrenocortical insufficiency in a patient with duodenal ulcer who had been ingesting soluble alkali for a prolonged period was reported as early as 1949 by Sawyer and Solez[3] and in 1951 by Rosenheim.[4] In 1954 Cheyne and Whithead[5] first described the association between the two syndromes. Such an association has appeared in a few case reports, the last that of Frank and Greenspan[6] in 1959.

Case Report

History

A 52-year-old male heavy-equipment operator was referred to Minneapolis Veterans Administration Hospital with hypercalcemia, recurrent acid-peptic disease, polyuria, polydipsia, weakness and muscle cramps. He gave a history of treating himself with large amounts of milk (one to one and a half gallons per day) and baking soda (one and a half pounds per month) for two and a half years prior to admission. He had discontinued ingesting baking soda six months prior to referral but continued drinking milk in lesser quantity (one to one and a half quarts per day). There was no history of vitamin D ingestion and apparently the milk powder he used to reconstitute and drink was not fortified with vitamin D. He described marked heat intolerance and muscle cramping while at work, for which he was advised by his physician to take salt tablets.

Examination

Temperature was 98.6°F., pulse rate, 112 per minute; blood pressure, 110/60 mm. Hg supine and 85/45 mm. Hg standing. He was pale, lethargic and weak. There was no hyperpigmentation in the skin or mucous membrane. No band keratopathy was observed on slit lamp examination. With the exception of mid-epigastric tenderness the rest of the physical examination was normal.

Laboratory Data

The patient was hyponatremic (natrium 123 mEq. per L.), normokalemic (4.8 mEq. per L.), hypercalcemic (calcium 11.3 mg. percent) and azotemic (blood urea nitrogen 86 mg. percent). Hemoglobin was 15.0 gm. per-

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cent on admission but fell to 12.3 gm. percent after hydration. Stool guaiac was positive. Arterial blood pH was 7.56. Serum phosphorus (3.5 mg. percent) alkaline phosphatase (14 kathode units), urinary calcium (106 mg. percent/24 hrs.), 17-OH and 17-ketosteroids, and x-rays of hands, jaw, feet and long bones were normal.

Other Studies

Upper gastrointestinal series showed hypertrophic gastric folds and an ulcer crater in the inferior recess of the duodenal cap. Gastric analysis yielded a basal acid secretion of 3 mEq. per hour which rose to 54 mEq. per hour after stimulation with 100 mg. of intramuscular betazole HCl (Histalog).

Kidney function tests indicated an inability to concentrate urine (sp. gr. 1.005-1.008). Urinalysis, culture, intravenous pyelogram and nephrotomogram and urinary calcium excretion while on controlled low calcium diet (100 mg./24 hrs.) were normal. Serum creatinine was 6.0 mg. percent and creatinine clearance was 13.3 cc. per minute. Twenty-four-hour urinary excretion of sodium on 200 mEq. natrium diet ranged between 112-176 mEq. per 24 hours. No determinations of fecal electrolytes were made.

A 21-day *calcium and phosphorus balance study* was initiated to exclude hyperparathyroidism and confirm the possibility of chronic milk-alkali syndrome. The diet during this period of study consisted of 300 mg. of calcium and 1000 mg. of phosphorus. Results are summarized in Figure 1.

The presence of heat intolerance, muscle cramps, weakness, postural hypotension, hyponatremia with improvement after salt replacement (Figure 2) suggested salt-losing nephropathy. A *natrium balance study* was designed to confirm this clinical impression. Results are summarized in Figure 3. On the tenth and eleventh days of this study the patient again was markedly symptomatic and it

Table

Salt-Losing Nephropathy. Review of Reported Cases (1944-1969)

Authors	Year of Publication	No. of Cases reported	Age	Sex	Underlying Cause	Course (as reported at time of publication)
Thorn et al.[1]	1944	2	21	M	Cystic disease of renal medulla	Died
			21	F	Chronic glomerulonephritis	Died
DeLa Balze & Onativia[21]	1947	1	34	M	Not determined	Died
Sawyer & Solez[3]	1949	1	53	M	Peptic ulcer, prolonged soluble alkali ingestion, tissue calcinosis	Died
Borst[20]	1950	1	42	M	Polycystic kidneys	Died
Rosenheim[4]	1951	1	55	M	Peptic ulcer, prolonged ingestion of soluble alkali	Alive
Nussbaum et al.[13]	1952	1	37	F	Chronic pyelonephritis	Died
Joiner & Thorne[14]	1952	3	21	F	Chronic pyelonephritis	Died
			18	M	Chronic pyelonephritis	Died
			27	M	Tubercular pyelonephritis	Died
Murphy et al.[22]	1952	1	30	M	Cystic disease of renal medulla	Died
Murphy et al.[16]	1953	4	35	M	Chronic glomerulonephritis	Died
			27	M	Chronic glomerulonephritis	Alive
			53	M	Chronic pyelonephritis	Alive
			25	M	Chronic glomerulonephritis	Alive
Milliez et al.[23]	1954	1	49	M	Peptic ulcer, "Nephritis of the ulcer patient," renal calcinosis	Died of myocardial infarction
Cheyne & Whithead[5]	1954	1	49	M	Peptic ulcer, prolonged ingestion of soluble alkali	Alive
Fongi et al.[24]	1954	1	53	M	Not determined, postgastrectomy	Alive
Gjorup et al.[25]	1954	1	36	M	Renal rickets, cause undetermined	Alive
Ericson et al.[15]	1955	2	52	M	Chronic pyelonephritis	Died
			27	F	Medullary cystic disease	Died
Levere & Wesson[26]	1956	1	29	M	Chronic glomerulonephritis	Alive
Knowles et al.[11]	1957	1	37	M	Peptic ulcer, prolonged ingestion of alkali and tissue calcinosis	Alive
Cleempoel & Karhausen[19]	1957	1	39	F	Chronic pyelonephritis	Died
Frank & Greenspan[6]	1959	1	50	M	Peptic ulcer, prolonged milk and alkali ingestion	Alive
Stanbury & Mahler[9]	1959	1	32	F	Not determined	Alive
Thorn et al.[28]	1960	2	27	F	Chronic pyelonephritis	Died
			37	M	Recurrent pneumonia	Alive
Falsetty & Kunin[27]	1963	6	8	—	Acute and chronic pyelonephritis	Died
			28	—	Diabetes mellitus, chronic pyelonephritis	Died
			61	—	Chronic pyelonephritis	Died
			54	—	Acute pyelonephritis	Alive
			61	—	Chronic pyelonephritis	Died
			62	—	Chronic pyelonephritis	Alive
Norredam, K.[17]	1966	1	37	F	Interstitial nephritis	Alive
Pertzov[18]	1966	1	28	F	Not determined	Alive
Ansari & Vennes	1969	1	53	M	Peptic ulcer, excessive intake of milk and alkali	Alive

was not possible to carry out further studies with administration of deoxycorticosterone acetate. However, Addison's disease was excluded by normal values of 17-OH and 17-ketosteroids determined on two different 24-hour urine collections.

Course in the Hospital

During his stay in the hospital the patient improved considerably under medical treatment. His serum calcium remained within normal limits. Rigorous antacid treatment with aluminum hydroxide gel required to relieve ulcer symptoms led to serum phosphorus depletion which was repleted by substitution of aluminum phosphate gel (Phosphaljel).

Although polyuria and inability to concentrate urine were still present on discharge there was some improvement in creatinine clearance (13 to 23 cc. per minute) and reduction in blood urea nitrogen (86-37 mg. percent). On a 300 mEq. natrium diet he had no symptoms of salt deficiency in the hospital but was advised to take extra salt while at work.

He became asymptomatic from his acid-peptic disease in 60 days and a repeat upper gastrointestinal series showed healing of the previous ulceration. Maximal acid output remained fixed (54 mEq. per hour) even after the serum calcium became normal.

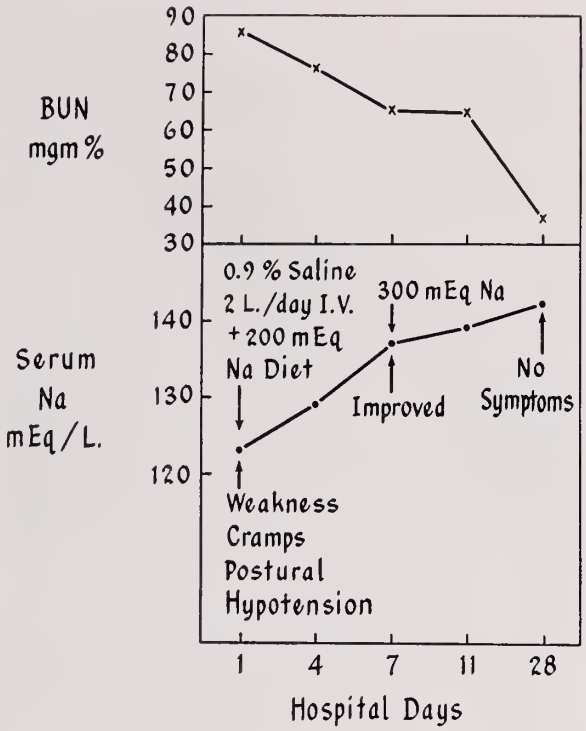


Figure 2—Depicts the relief of symptoms and decrease in azotemia with correction of hyponatremia.

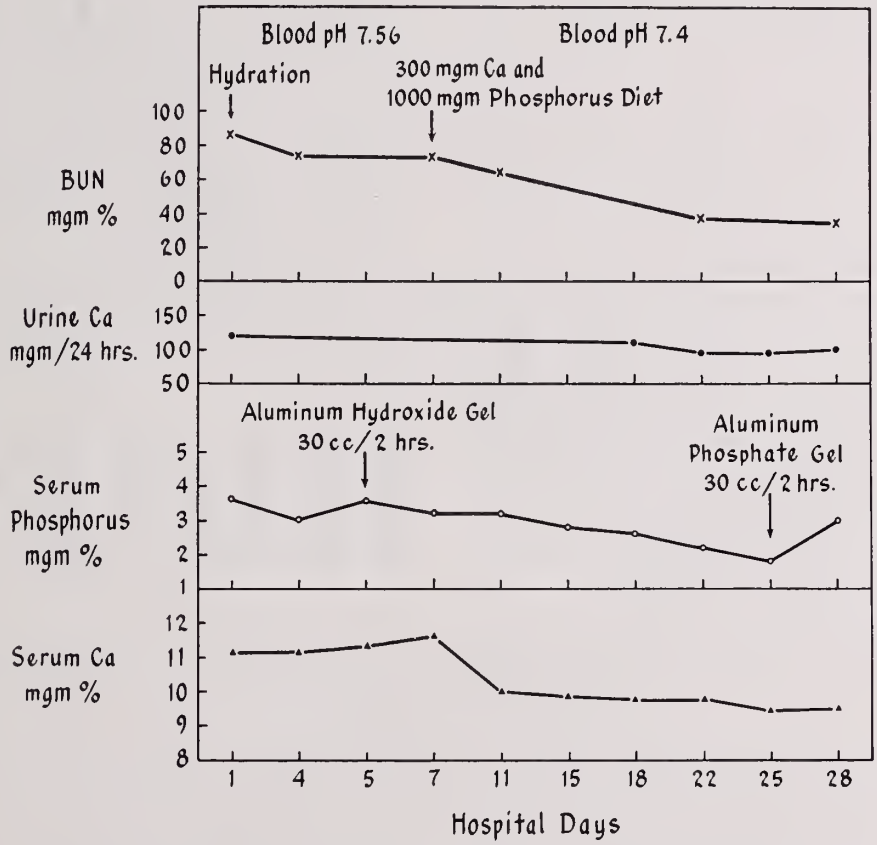


Figure 1—Graphic representation of the laboratory findings before and after low Ca, low phosphorus diet and hydration.

Discussion

Hypercalcemia and Renal Insufficiency

Hypercalcemia and renal insufficiency are seen in a variety of disease states such as hyperparathyroidism, sarcoidosis, multiple myeloma, hypervitaminosis D, acute osteoporosis, Addison's disease, chronic milk-alkali syndrome, generalized carcinomatosis with or without evidence of metastasis. In our patient the history of ingestion of excessive amounts of milk and soluble alkali, hypercalcemia without hypercalciuria or hyperphosphaturia, blood pH of 7.56, normal serum phosphorus and alkaline phosphatase with no evidence of skeletal involvement suggested that chronic milk-alkali syndrome was the underlying cause of his hypercalcemia and impaired renal functions. Normalization of serum calcium and blood pH and reduction in azotemia on withdrawal of milk with substitution of a low calcium diet further confirmed the clinical impression; however, it should be noted that unlike other cases of chronic milk-alkali syndrome, features such as pruritis, band keratopathy, tissue calcinosis and hyperpigmentation were not seen in our patient.

Inability to Concentrate Urine

Impairment of renal function was indicated by inability to concentrate urine, elevated blood urea nitrogen, serum creatinine and low creatinine clearance. Although nephrocalcinosis was not seen on tomography, it cannot be excluded in the absence of kidney biopsy. The ingestion of excess soluble alkali and milk contributed significantly to renal impairment and was primarily responsible for the chronic renal insufficiency in this case.

There are two important nephrotoxic factors responsible for the onset of renal failure in chronic milk-alkali syndrome. These are (1) metabolic alkalosis and (2) hypercalcemia. Metabolic alkalosis itself has been shown to result in renal insufficiency[7], probably by augmenting calcium deposition in the renal parenchyma as was seen

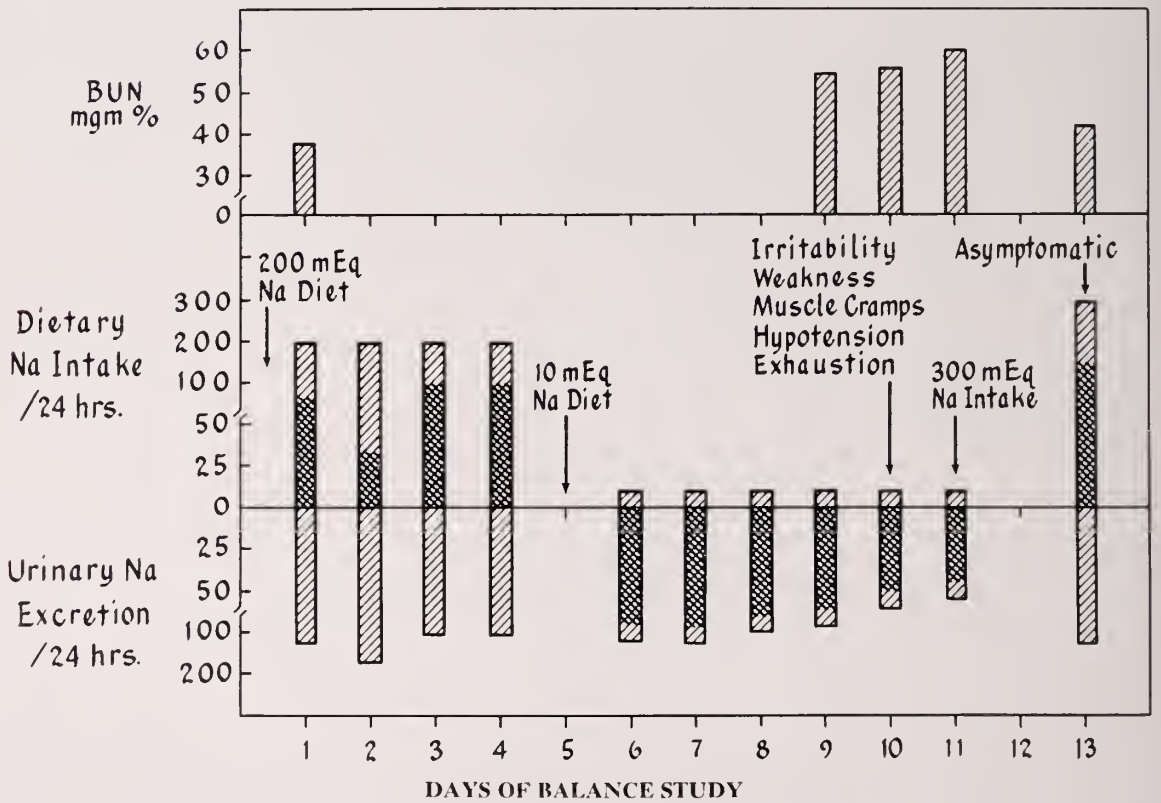


Figure 3—Studies on Natrium balance before, during and after Natrium restriction. Cross-hatched areas indicate Natrium balance, i.e., difference between intake and urinary output. On days one to four the intake of Natrium is 200 mEq. per day and on days five to 10, Natrium is restricted to 10 mEq. per day. Note that patient remained in positive Natrium balance on days one to four and entered negative Natrium balance on days six to 10. Signs, symptoms and azotemia which developed on day 10 reverted to normal after three days of increased Natrium intake.

in the case of Sawyer and Solez.[3] Increased serum calcium may be just an additional determining factor. The pathogenesis and diverse clinical manifestations of patients with chronic milk-alkali syndrome are well reviewed by Randall and his associates.[8] Falsetty and Kunnin[27] isolated *Pseudomonas aerogenosa* in 50 percent of their salt-losing nephritis patients; they postulated that the bacteriuria may damage renal tubules and interfere with tubular reabsorption of sodium. This finding, however, has not been confirmed by others. A critical review of their data reveals that renal wastage of sodium was not excessive in at least three to four of their patients although they were designated as having "salt-losing nephritis."

Clinical Manifestations

The initial findings of weakness, muscle cramps, postural hypotension, elevated blood urea nitrogen, hypercalciuria, hyponatremia, hypernatriuria, normal serum potassium and good response to saline infusion may suggest Addison's disease. However, absence of pigmentation, normal urinary K, normal libido and blood pressure after an initial episode of hypotension, normal urinary 17-OH and 17-ketosteroids and normal serum calcium in the early part of the course without any replacement therapy by corticosteroids exclude hypoadrenalism and confirm the existence of salt-losing nephropathy. This was further documented by the sodium balance study (Figure 3). The patient's precarious clinical state on the fifth and sixth days after salt restriction prevented us from further study of the effect of deoxycorticosterone acetate on natrium excretion.

Therapy

The development of salt-losing nephritis is commonly accounted for by invoking a specific defect in distal renal tubular function. Thorn et al. first invoked this postulate to explain the ineffectiveness of deoxycorticosterone acetate to conserve natrium excretion on a low natrium diet. Stanbury et al.[9] emphasized that failure of deoxycorticosterone acetate to reduce urinary output of sodium in salt-losing nephritis is by no means indicative of a specific "tubular unresponsiveness," as has been commonly supposed. Azotemic patients not sustaining larger doses of salt have also failed to conserve natrium during deoxycorticosterone acetate administration[10]; moreover, a demonstrable response cannot logically be expected when endogenous production of aldosterone is greatly increased, as was shown by Stanbury et al.[9]

Patients with chronic renal insufficiency and salt-losing nephropathy may respond to decrease in salt intake by a fall in urinary volume and reduction in the excretion of natrium. The concentration of natrium in urine is reduced because of decrease in filtered load and increased reabsorption of sodium by the tubules. The output of urinary sodium may fall to the level of dietary intake with the establishment of a new external equilibrium in a state of sodium deficiency. Knowles et al.[11] indicated that such an extensive balance was achieved in their patient on the sixth and seventh days of reducing the dietary intake of sodium. This certainly was not seen in our patient, as he remained in considerable negative balance even on the sixth day. This probably reflects a considerable degree of impairment of sodium conservation, as the normal kidney should excrete very little or no sodium on a 10 mEq. natrium diet and achieve external balance much earlier.

Etiology

It is well known that patients with chronic renal failure of any etiology not infrequently develop a deficiency of sodium.[12] Because of this general tendency, it has been suggested that salt-losing nephropathy should not be considered a separate entity. However, it is convenient and important to retain the term for at least two reasons: (1) better definition of a clinical syndrome and (2) its therapeutic implication. A deficiency of sodium and the symptoms resulting therefrom in patients with chronic renal failure of any etiology is seen when the dietary intake of sodium is restricted. In patients with salt-losing nephropathy, hyponatremia and symptoms of sodium deficiency occur even when the intake of sodium is normal; and such patients invariably require additional sodium supplement because their disability lies in the extreme impairment of sodium conservation.

The relationship between chronic milk-alkali syndrome and salt-losing nephropathy has been suggested previously[3] but not adequately emphasized; it therefore remains unappreciated to date.

Six other patients similar in many aspects to

the one described above have been reported in the world's literature since 1944. All were male, aged 49 to 53 years, and had certain clinical features in common. The basic underlying disorder was acid-peptic disease for which they had ingested large amounts of soluble alkali for years. All developed renal insufficiency and salt-losing nephropathy subsequently. In five patients the description is quite suggestive of chronic milk-alkali syndrome, but no mention of excess calcium intake is made nor were the serum calcium and pH measured. One such patient had tissue calcinosis at autopsy. The absence of history of excess calcium intake in these patients should not be disturbing because it is probable that the milk intake was significant though not recorded.

At the time of this report about 50 cases of chronic milk-alkali syndrome have been described in the literature during the past 20 years. Fourteen percent (7/50) of the patients are reported to have salt-losing nephropathy in addition.

Review of salt-losing nephropathy for the past 25 years (1944-1969) reveals that only 37 patients have been described (Table). Sex ratio was 1.1:1. Seventy-five percent (28/37) of the patients had a primary renal disease as the underlying cause; in 19 percent (7/37) involvement of the kidneys was secondary to peptic ulcer. Excessive ingestion of alkali and/or milk-alkali was the only outstanding cause. This association is probably significant.

Prognosis

Prognosis in salt-losing nephropathy is poor. Fifty percent of the patients were dead at the time of publication. However, it appears that prognosis is much better in patients with chronic milk-alkali syndrome. Death was related to this cause in only one patient—a mortality of 14.6 percent (1/7); one other died of totally unrelated cause. Mortality was significantly higher (60 percent) in patients with a primary renal disease as the underlying cause. The better prognostic outlook in patients with chronic milk-alkali syndrome may be due to the fact that the underlying cause is potentially reversible if recognized and treated early.

Salt-losing nephritis may not be as rare as it seems to be from review of the literature. With due attention to patients' symptoms and, when indicated, sodium balance studies, it is likely that this entity will be recognized more often.

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It does not take great men to do great things; it only takes consecrated men.
—Phillips Brooks

Sarcoidosis

Associated with Regional Enteritis (Crohn's Disease)

Report of Two Cases

DAVID E. DINES, M.D.,* RICHARD A. DeREMEE, M.D.* AND PAUL A. GREEN, M.D.*

NONCASEATING GRANULOMA consistent with Boeck's sarcoid may be a common response to numerous agents and diseases. We have seen two patients who had sarcoidosis associated with regional ileitis (Crohn's disease). Both may have had two diseases, or they may have had a granulomatous reaction that represented a generalized host response with overt manifestations localized in the lungs and gastrointestinal tract. Because the association of sarcoidosis and regional ileitis is unusual, Boeck's sarcoid may be a host response to numerous and diverse agents rather than a distinct disease entity of singular cause.

Report of Cases

Case 1

A 44-year-old man was seen on August 1, 1968, because of swelling and stiffness of his joints. At the onset of swelling in the fingers and knees, he also noticed subcutaneous nodules over his forearms and legs. Biopsy of one of the nodules revealed noncaseating granuloma. He had been at the Mayo Clinic one year previously, with a history of diarrhea and crampy abdominal pain since 1952. A roentgenogram of the small bowel on July 24, 1967 (Figure 1 *A*), had shown regional ileitis. On December 26, 1967, a resection of the cecum, appendix, and a portion of the ileum, with an ileo-ascending colostomy (end-to-end) had been done because of regional enteritis of the distal ileum. The specimen showed severe, chronic, regional enteritis involving the distal 38 cm of the resected segment of the ileum. The affected regions showed thickening of the wall, confluent ulcers, and narrowing of the lumen. Granulomas were present. All cultures had been negative for atypical mycobacteria and *Mycobacterium tuberculosis*.

Physical examination on August 1, 1968, revealed subcutaneous nodules of both forearms but no supraclavicular adenopathy, and the lungs were clear. The liver and spleen were not palpable.

A roentgenogram of the chest on August 5, 1968, showed discrete, finely nodular infiltrates throughout

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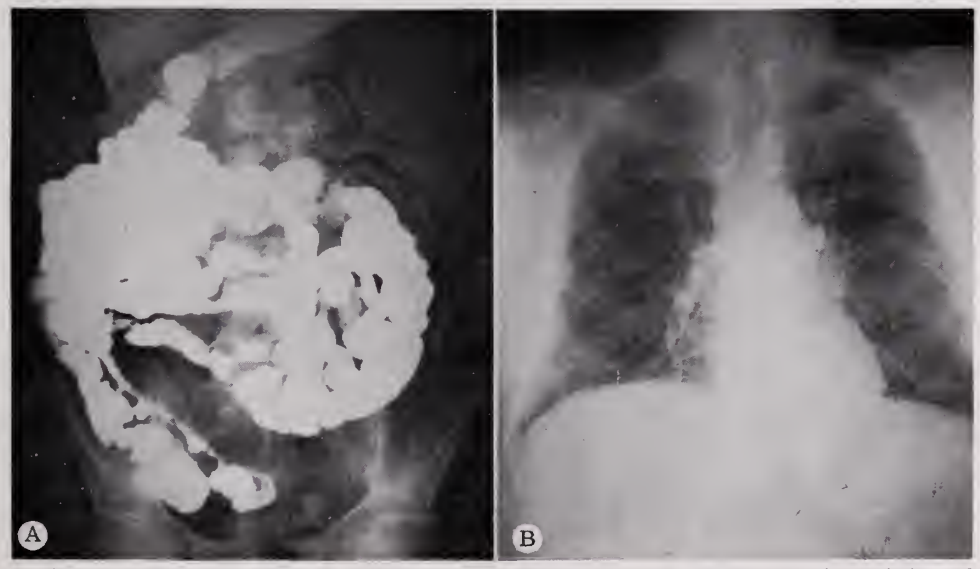


Fig. 1 (Case 1)—*A*, Small bowel roentgenogram (July 24, 1967) shows regional ileitis of distal ileum. *B*, Chest roentgenogram (August 5, 1968) shows a discrete, finely nodular infiltration diffusely throughout both lung fields.

both lungs (Figure 1 *B*). Roentgenograms of the small intestine did not show signs of recurrent Crohn's disease. Induced sputum and gastric cultures were negative for acid-fast bacilli. Tuberculin skin tests of first and second strengths were nonreactive. Lupus erythematosus (LE) clot preparation was negative, and values for hemoglobin, leukocyte count, and sedimentation rate were normal. Sulfobromophthalein retention was 8% in one hour. Pulmonary function tests showed normal lung volumes, with the vital capacity of 5 liters and a total capacity of 7.5 liters. Oxygen saturation was normal both at rest and after five minutes of exercise. The CO-diffusing capacity was 23 ml/min/mm Hg (normal 24 to 41).

A transbronchoscopic lung biopsy showed noncaseating granuloma.

Case 2

A 51-year-old man was seen on November 1, 1968, because of chronic cough of 16 years' duration. Since 1944, roentgenograms have shown bilateral hilar adenopathy with perihilar fibrotic changes. In 1961 he had had diarrhea with crampy abdominal pain. Regional enteritis was diagnosed, and laparotomy in December 1961 resulted in resection of the involved ileum and adjacent colon. At that time obstructing regional ileitis was diagnosed, and the lymph nodes showed inflammatory changes. Cultures were negative. The patient had been taking 10 mg of prednisone each day since 1963, without further severe flare-ups of the regional enteritis. A scalene node biopsy in 1966 showed inflammatory changes.

Examination revealed no adenopathy, clear lungs, and no hepatosplenomegaly.

No abnormalities were noted for the following: urine, hemoglobin, leukocyte count, sedimentation rate, blood sugar, urea, calcium, and protein electrophoretic pattern. The lupus erythematosus preparation was negative. A roentgenogram of the chest (Figure 2 *A*) showed a diffuse interstitial process throughout each lung and hilar adenopathy; and a roentgenogram of the small intestines (Figure 2 *B*) showed recurrent regional enteritis involving a short segment of the ileum about four inches long, proximal to the side-to-side ileotransverse colostomy. Induced sputum and gastric cultures were negative for tuberculosis and fungi. A tuberculin skin test, first and second strengths, was nonreactive. Pulmonary function tests showed normal lung volumes, normal maximal breathing capacity and midexpiratory flow rate, and normal arterial oxygen saturation. The CO-diffusing capacity was 21 ml/min/mm Hg (normal 22 to 38).

Discussion

The cause of sarcoidosis as well as that of regional enteritis is not known. Although the granulomatous lesions seen in both conditions are virtually identical, their existence does not provide convincing evidence of a common cause. Furthermore, Fletcher and Hinton's study[1] of Crohn's disease did not show depression of tuberculin reactivity such as is seen in sarcoidosis. More recent studies, however, suggest that the immunologic response in sarcoidosis is similar to that in regional enteritis.[2] In 10 of 26 patients with Crohn's disease, delayed hypersensitivity to 100 TU of old tuberculin failed to develop. In addition, delayed hypersensitivity did not develop to dinitrochlorobenzene, a potent allergen. Reactions of patients with sarcoidosis were similar.[3] Further evidence of a similar immunologic response in the two disorders is suggested by the work of Mitchell and associates.[4] Of 48 patients with Crohn's disease, 24 had positive Kveim test

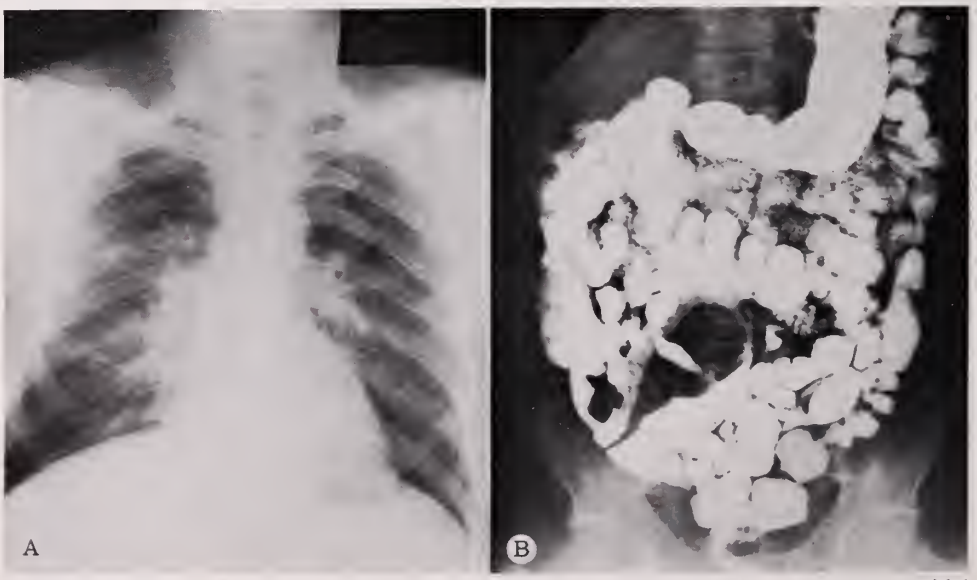


Fig. 2 (Case 2)—*A*, Chest roentgenogram (October 29, 1968) shows a diffuse interstitial process throughout both lungs (more on the right) and hilar adenopathy. *B*, Small bowel roentgenogram (November 1, 1968) shows a recurrent regional enteritis involving a short segment of ileum.

reactions, as demonstrated microscopically by typical granuloma formation in specimens taken from the site of antigen injection. The authors postulated that there was either a cross-reactivity between sarcoidosis and Crohn's disease antigens or an etiologic agent common to the two diseases.

Previous work by Chapman and associates[5-7] has established the presence of antibodies against atypical mycobacteria in the serum of some patients with sarcoidosis. They have presented further evidence that indicates that IgA antibodies in sarcoidosis may represent new formation of antibodies, either as a regular stage in the production of atypical mycobacterial antibodies or as a feature of granuloma formation, or as both. Recently, Sokolowski, Schillaci, and Motley[8] reported a patient with disseminated cryptococcosis complicating sarcoidosis. Noncaseating granulomas were seen on cervical node biopsy, and there was histologic and serologic identification of Runyon group II scotochromogen, suggesting a relationship of sarcoidosis to the atypical myocobacterium, as developed by Chapman. However, disseminated cryptococcosis has been reported as eliciting a generalized sarcoid reaction by itself[9] and, as mentioned previously, we really do not know whether the noncaseating granuloma of sarcoidosis is a common response to numerous agents and diseases. Both an infectious agent and altered immunity may be important in producing granulomas.

Both patients had regional enteritis at surgery. One had granulomas, and the other had inflammatory changes of the mesenteric lymph nodes. In both, cultures were negative. The patient of Case 1 had biopsy-proved noncaseating granuloma of a subcutaneous nodule and noncaseating granuloma on transbronchoscopic lung biopsy. Cultures were negative for atypical and acid-fast bacilli. The diagnosis of sarcoidosis in the second case was a presumptive one. This patient has had bilateral hilar adenopathy with diffuse interstitial fibrotic changes since 1944, without progression. It seems reasonable that only a truly benign condition like sarcoidosis could exist this long without causing symptoms.

The concept that sarcoidosis occurs in association with an unusual kind of immunologic responsiveness is not new. Pinner[10] was the first to suggest that sarcoid was an anergic form of tuberculosis. Mankiewicz and Van Walbeek[11] first demonstrated that patients with sarcoidosis and tuberculosis excrete large quantities of phage that are lytic to virulent mycobacteria in their stool. It has been shown that susceptible persons with phage-infested mycobacteria respond immunologically to both mycobacteria and phage antigens. It has been postulated that the production of phage-neutralizing antibodies impairs the effectiveness of the phage, and clinical infection with acid-fast bacilli develops. If the patient is unable to stimulate an effective immunologic response to the phage, typical tubercle bacilli do not develop and an altered phage-resistant mycobacterium is seen. Areas of chronic granulomatous inflammation, free of caseous necrosis, not associated with tuberculin hypersensitivity, but typical of clinical sarcoidosis, develop. In this hypothesis, an infectious agent and altered immunity are both important to the pathogenesis of sarcoidosis.[12] In our two cases, studies of phage and immunoglobulins were not done.

If noncaseating granulomatous reaction (sarcoid reaction) represents a normal host-defensive response to many and varied agents, the rare association of a generalized sarcoid reaction and a localized one in the ileum raises some interesting possibilities. The two major portals of entry for most injurious substances, namely, the gastrointestinal and respiratory tracts, may be mutually protective in some way. In the case of the usually encountered sarcoid reaction affecting the respiratory tract, the theoretic provocative agent or agents might gain access to the body at this portal of entry, thus inciting the sarcoid reaction in and along the contiguous sites of inoculation. The sarcoid reaction, in turn, may protect the other main portal of entry, namely, the gastrointestinal tract. The converse sequence of events likewise may hold true. The coexistence of sarcoidosis and Crohn's disease in the same patient may suggest that a provocative agent entered the respiratory and gastrointestinal tracts simultaneously, the synchrony of inoculation then leaving both organs unprotected.

Summary

Two cases of sarcoidosis associated with regional ileitis (Crohn's disease) have been presented. Both patients may have had two different diseases or they may have had one disease representing a specific host response that manifested

synchronously in the respiratory and gastrointestinal tracts.

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Nature's Sink For Carbon Monoxide

An estimate of the total capacity of the soil to remove carbon monoxide from the atmosphere is ascribed to the activity of the soil micro-organisms. From the study at the Stanford Research Institute the average activity of the soil was 8.44 mg of carbon monoxide per hour per square meter of soil. This would be equivalent to 191.1 metric tons per year per square mile. Calculating further—the capacity of the total soil surface of the continental United States for removing carbon monoxide from the atmosphere is estimated to be 569 million metric tons per year, which is 6.5 times the annual estimated production of carbon monoxide attributed to the United States. The soil, therefore, can be considered as a major natural sink for carbon monoxide that is released into the atmosphere by natural emitters or by the burning of fossil fuels.*

*Science, 1972: 3989: 1229, June 18, 1971.

Editor's Note: What a relief! Let's clean up but no need to panic! Some of the catastrophians seemed to suggest that we were breathing our last. Incidentally, it was observed that the San Bernardino Freeway, the Mojave Desert and a few other areas with low content of organic matter, had a much lower capacity for removing carbon monoxide.

TODAY

"Write it on your heart that every day is the best day in the year. He is rich who owns the day, and no one owns the day who allows it to be invaded with fret and anxiety. Finish every day and be done with it. You have done what you could. Some blunders and absurdities, no doubt, crept in. Forget them as soon as you can, tomorrow is a new day; begin it well and serenely, with too high a spirit to be cumbered with your old nonsense. This new day is too dear with its hopes and invitations, to waste a moment on the yesterdays."—Ralph Waldo Emerson



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A triumph over trichomoniasis

The male urogenital tract is by far the main source of reinfection in trichomonal vaginitis.

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Because of published reports of consistently high cure rates—often up to 100 percent—and a relatively low incidence of side effects, Flagyl has become the agent of choice for trichomonal vaginitis.

Indications: For the treatment of trichomoniasis in both male and female patients and the sexual partners of patients with a recurrence of the infection provided trichomonads have been demonstrated by wet smear or culture.

Contraindications: Evidence of or a history of blood dyscrasia, active organic disease of the central nervous system and the first trimester of pregnancy.

Warnings: Use with discretion during the second and third trimesters of pregnancy and restrict to patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, vomiting and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. There is no accepted proof that Flagyl is effective against other organisms and it should not be used in the treatment of other conditions. Exacerbation of moniliasis may occur.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry or sore tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Monilia*, exacerbation of vaginal moniliasis, an occasional reversible moderate leukopenia, dizziness, vertigo, drowsiness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, dryness of the mouth, vagina or vulva, vaginal burning, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, nasal congestion, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified.

Dosage and Administration: *In the Female.* One 250-mg. tablet orally three times daily for ten days. Courses may be repeated if required in especially stubborn cases; in such patients an interval of four to six weeks between courses and total and differential leukocyte counts before, during and after treatment are recommended. Vaginal inserts of 500 mg. are available for use, particularly in stubborn cases. *When the vaginal inserts are used* one 500-mg. insert is placed high in the vaginal vault each day for ten days and the oral dosage is reduced to two 250-mg. tablets daily during the ten-day course of treatment. Do not use the vaginal inserts as the sole form of therapy. *In the Male.* Prescribe Flagyl only when trichomonads are demonstrated in the urogenital tract, one 250-mg. tablet two times daily for ten days. Flagyl should be taken by both partners over the same ten-day period when it is prescribed for the male in conjunction with the treatment of his female partner.

Dosage Forms: Oral tablets 250 mg.
Vaginal inserts 500 mg.

References available on request.

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Editorials

Antenatal Evaluation of the Fetus

It is well recognized that there is an association between low birth weight and perinatal mortality. However, fetal weight which appears disproportionately low for gestational age does not necessarily mean that the menstrual history is inaccurate and the fetus immature. Because fetal maturity is a function of gestational age, accurate evaluation of the latter assumes special importance in some situations. The report of Jools et al. in this issue confirms the usefulness of amniotic fluid studies when gestational age is in doubt. It should be reemphasized that laboratory determinations are only part of the overall evaluation and must be placed in the proper perspective and interpreted in the light of clinical findings.

Early prenatal care should be emphasized. An accurate menstrual history, particularly when menstrual intervals vary or are prolonged, must be taken and considered as the pregnancy progresses. At the present time, when families are smaller and a greater proportion of pregnancies are planned, the physician should consider the patient's recording of basal body temperatures during the cycles when conception may occur to pinpoint the time of conception. This technique is especially important among women who discontinue oral contraceptive agents in anticipation of conception. "Oversuppression" is a common phenomenon among these women and the time of ovulation is extremely variable. With basal body temperature documentation of the time of ovulation the duration of gestation is never in doubt. This information is of great help in evaluation of the high-risk patient.

Uterine size in early gestation is relatively consistent with the duration of the pregnancy. The physician should ask the patient to record the time fetal movements are definitely noted. This is usually at about 18 weeks' gestation. Similarly, the fetal heart rate can be detected with a fetoscope at approximately 20 weeks' gestation. Discrepancies of these dates with the duration of amenorrhea should be noted.

Careful measurement and recording of uterine size at each prenatal visit is also of great importance to detect fetal growth retardation. This is best accomplished by measuring the height of the fundus above the symphysis pubis, with either a measuring tape or a pelvimeter. When the latter is used, it should be checked for accuracy in the full range. In addition to cessation of uterine enlargement, which is usually accompanied by a decrease in the quantity of amniotic fluid, a lack of maternal weight gain should alert the physician to the possibility of abnormal fetal growth.

A fetogram may be helpful but will rarely show the distal femoral epiphyses prior to the 36th or 37th week of gestation. It will, however, occasionally demonstrate a fetal abnormality or detect an unrecognized twin gestation.

A recent and promising finding suggests that the lecithin content of amniotic fluid is directly proportional to the maturity of the fetal lungs and the presence of surfactant. The latter is believed to prevent collapse of the alveoli. When

a critical concentration of lecithin is present, the incidence of the respiratory distress syndrome is reported to be very low, and induction or cesarean section can safely be considered.

Amniotic fluid studies may be of value in a different situation, where the fetus is possibly in jeopardy from Rh isoimmunization, diabetes, toxemia or placental insufficiency. The determination of amniotic fluid bilirubin in assessing the status of the fetus who has erythroblastosis has been well established and is now accepted by all obstetricians. The recognition of subacute fetal distress by the dark appearance of amniotic fluid obtained by amniocentesis or as seen through the slightly dilated cervix with the amnioscope is also possible.

Information can be obtained from amniotic fluid, but to determine whether the fetus is safer in utero or in a premature nursery requires fine clinical judgment. Interruption of the pregnancy may be indicated when accurate evaluation of the duration of gestation and the status of the fetus has been made. In such situations, careful monitoring of a fetal heart rate is necessary if the patient is in labor. Cesarean section to avoid the additional stress of labor may be indicated to prevent further insult to an already compromised fetus.

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Genesis and Treatment of Gallstones*

Fifteen to 20 million people in the United States have gallstones.[1] Bile acids and lecithin are the primary solubilizing agents for cholesterol in bile, and in this country gallstones are composed predominantly of cholesterol.[2] Bile is lithogenic when its physicochemical state is such that the concentration of either or both of these solubilizing agents is sufficiently decreased relative to cholesterol to result in crystallization or liquid crystallization of cholesterol, or in supersaturation or saturation with cholesterol.[3]

Patients with gallstones have a decreased ratio of bile acids and lecithin to cholesterol in hepatic as well as gallbladder bile,[4,5] and they also have a decreased bile acid pool size.[6] Lithogenic bile, often with ratios surpassing the limits of micellar solubilization of cholesterol, has been found among young American-Indian women without gallstones, a high-risk group for cholelithiasis.[7] Thus, secretion of lithogenic hepatic bile appears to be the prerequisite abnormality for the growth and maturation of gallstones.[8] The hepatic enzymatic abnormalities causing the secretion of lithogenic bile should be sought.[9] These new observations have further stimulated investigation to induce alterations in bile favorable for the dissolution of gallstones.

Rewbridge[10] and later Cole and Harridge[11] noted the disappearance of gallstones after administration of crude bile salts in humans, but their observations were uncontrolled and bile analyses were not done. Swell and Bell[12] administered proprietary bile salt preparations and found increased ratios of biliary bile acid and phospholipid to cholesterol in two of three patients with T tubes after cholecystectomy. Tompkins and co-workers[13] noted an increased lecithin to cholesterol ratio and an increased cholesterol-holding capacity after feeding soybean lecithin with a low-fat diet to postcholecystectomy patients with T tubes. Individual pure bile acids have been fed to humans with cholelithiasis without interruption of the enterohepatic circulation. Chenodeoxycholic acid, but not cholic acid, significantly increased the ratio of bile acids plus lecithin to cholesterol and decreased the lithogenic potential of bile in these patients with cholelithiasis[14] and in young Chippewa women without gallstones, a group likely to manifest a high incidence of gallstones.[7] Although the prevention or dissolution of gallstones has not yet been achieved, significant progress has been made.

Thus, Dr. Hordinsky's report, "Terpenes in the Treatment of Gallstones,[15]" concerns a topic of vital and current interest. Rowachol, a combination of volatile oils containing the hydrocarbon terpene ($C_{10}H_{16}$) or a polymer of it, is a strong choleretic. Based on the rationale that increasing bile flow might facilitate fragmentation of gallstones, Rowachol was administered for six months to 151 patients with cholelithiasis. Cholecystography revealed that the gallstones had disappeared

*See page 649.

n four of the patients. Unfortunately, the significance of this observation is muted because control subjects with cholelithiasis, either untreated or given another choleretic agent, were not included. Disappearance of gallstones by spontaneous dissolution or passage through the bile duct, although rare, is well documented.[16] In regard to the use of choleretics to dissolve gallstones, although the relevance of animal studies to man is uncertain, choleretics have not prevented or dissolved these gallstones.[17] Moreover, mice fed 0.5% dehydrocholate (Decholin), albeit not other choleretics, developed cholelithiasis.[18] Finally, data on biliary lipid composition in response to the terpenes are important and not yet available.

The idea of medical dissolution of cholesterol gallstones has advanced to the realm of feasibility and should be vigorously pursued.

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References may be secured from the author.

Consequences of Antacid Therapy*

In addition to the cultural, political, and social labels applied to our culture, the term "Medicated Society" has been used. One basis for this appellation is man's various dyspeptic syndromes, both real and those created by TV commercials, which are responsible for the often inappropriate consumption of alkalis and antacids in quantities which must approach the tons of salicylates and laxatives used by modern man. In addition, the chronic, recurrent nature of peptic ulcer and the importance placed on neutralization of acid in its medical management ensure the more or less regular ingestion of antacids and the at least theoretical risk of a variety of physical and metabolic consequences of their use. The patient described by Dr. Ansari in the August, 1970, issue of *Minnesota Medicine* exemplifies two such complications, and his study sheds new light on one of these.

The earliest antacid agents were the absorbable alkalis such as sodium bicarbonate and calcium and magnesium carbonates. Although the first is no longer prescribed in ulcer therapy, many persons acquire the "baking soda habit" and physicians still encounter systemic alkalosis resulting from the regular and excessive ingestion of sodium bicarbonate and other alkaline salts. The milk-alkali syndrome, consisting of hypercalcemia without hypercalciuria but with renal insufficiency and calcinosis, may complicate the course and therapy of ulcer disease in patients with excessive intake of milk and absorbable alkali over long periods. Hypercalcemia per se has been shown to occur in up to 20% of persons making regular heavy use of calcium carbonate. More recently, ingestion of calcium carbonate has been shown, in humans, to be followed by increased gastric secretion ("acid rebound"). The mechanism has been ascribed by one observer to the action of calcium ions within the gastrointestinal tract, and by others to transient hypercalcemia which has been shown to induce gastrin release at least under certain conditions.

The introduction of so-called nonabsorbable antacids, principally salts and bases of aluminum and magnesium, has helped to decrease greatly the risks of these therapeutic complications. However, even these antacids are not without their side-effects, some of which are due to their chemical composition and others, to certain physical characteristics and to special circumstances. Every physician is aware of the constipating effect of aluminum hydroxide preparations and the likelihood of magnesium compounds to induce diarrhea. Magnesium toxicity (neurologic, neuromuscular, and cardiovascular impairment) has been observed in patients receiving magnesium antacids in the presence of greatly decreased renal function. The sodium content of many antacid preparations is such that, when they are used in the presence of conditions in which sodium retention occurs, edema or other undesirable consequences of fluid retention may result.

Other side-effects of antacid therapy have been the formation of intestinal casts or impactions of blood and antacid when the latter was used

*Ansari, A.: Antacid-Induced Phosphorus Depletion and Repletion. Minnesota Med 53:837, 1970.

vigorously in the medical treatment of hemorrhage from duodenal ulcer. Obstruction of the small intestine from a mass of proprietary antacid tablets—still recognizable and undissolved in the bowel lumen—has occurred, as well as at least one instance of development of silicious renal stone after prolonged use of magnesium trisilicate.

The production of a phosphorus-depletion syndrome in man is probably one of the least recognized consequences of antacid therapy, although the intestinal binding of dietary inorganic phosphate by aluminum hydroxide was observed soon after its introduction as a nonabsorbable antacid. Furthermore, it was shown soon thereafter that use of aluminum phosphate could avoid this phenomenon; but this antacid has never achieved popularity or widespread clinical use. The syndrome has been experimentally induced in normal humans and in patients with hypoparathyroidism or pseudohypoparathyroidism by prolonged, excessive ingestion of aluminum and magnesium hydroxides. The essential biochemical derangements consisted of hypophosphatemia, hypophosphaturia, increased gut absorption of calcium, hypercalciuria, and increased bone resorption. The symptoms usually noted are debility, anorexia, weakness, malaise, and bone pain. In one instance, overt osteomalacia in association with this syndrome appeared to be attributable to antacid-induced phosphorus depletion.

Under the usual clinical circumstances of peptic ulcer and its medical treatment, it is no doubt very uncommon that significant phosphorus depletion will be encountered, because most patients usually have a high phosphate intake (milk) as part of the therapeutic regimen. However, it is conceivable that, in patients not taking milk, intolerant of milk, or otherwise limited in their dietary phosphate intake, this syndrome may arise. The case reported by Ansari is of particular interest for several reasons. It exemplifies two complications of medical treatment of peptic ulcer. The patient initially was found to have a self-induced chronic milk-alkali syndrome as a result of the consumption of large quantities of milk and baking soda. The measures used to correct this problem included a low-calcium diet which, of necessity, entailed significant restriction of dietary phosphate also. The patient's persistent peptic ulcer symptoms required continued antacid therapy with aluminum hydroxide, with the result that phosphorus depletion ensued. Of interest was the repletion of phosphorus by the use of aluminum phosphate as an antacid.

The current tempo of our time is charged with growing concern, approaching a sense of crisis, for our environment and its preservation against man-made pollution and destruction. In many instances, physicians are leaders in this ecologic crusade. We must not forget that the rest of society considers the medical profession its mentor and guide in the preservation of man's internal health and environment. Just as the use of an insecticide, weed killer, or agricultural fertilizer, or the dumping of industrial wastes into a stream can have far-reaching consequences which have been tardily appreciated, so can virtually every therapeutic agent administered by physicians have its untoward consequences, including the use of seemingly innocuous antacids and alkalis in the treatment of peptic ulcer or what the television commercial calls "acid indigestion."

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Treatment of Peptic Ulcer

In his reappraisal of the problem, Piper* expresses certain concepts about the diagnosis and treatment of peptic ulcer. Anyone who engages in such a discussion is going to encounter conflicting opinions among his colleagues in this field. The vagaries of peptic ulcer, particularly when one is trying to appraise the value of any facet of medical treatment—diet, bed rest, the use of anticholinergics or antacids, the interdiction of smoking, and the control of psychic and emotional stress—are such that dogmatism is best avoided. Evaluating the effects of one facet of treatment while controlling all the others is a most difficult task. The healing or the persistence of a gastric ulcer can be followed well by x-ray examination and by gastroscopy. The reaction

*Piper, D. W.: The Treatment of Peptic Ulcer: A Critical Appraisal. Minnesota Med 54:387, 1971.

of a duodenal ulcer is less amenable to such procedures. In my opinion extensive double-blind studies are needed before one can discard the old as being useless or adopt the newer methods of medical treatment as being more effective than the old.

Essentially, duodenal ulcer is always benign. But any gastric ulcer, no matter how small or how large, should be considered potentially malignant until it has completely healed, disappears, and does not reappear on repeated examination for a year. I would, therefore, have preferred that the author had made a clearer separation of these two types of ulcer when he discussed evaluation and treatment.

While Piper states that the use of exfoliative cytology, gastric biopsy, gastroscopy, and gastric secretion studies ". . . should leave no doubt as to whether a gastric lesion is benign or malignant" (describing only one case in which use of these procedures left some doubt), the number of cases studied is not mentioned. The statement that ". . . exfoliative cytology will give false negative results in 30% of patients suffering from malignant ulcer" must leave some doubt in the reliability of any criterion of malignancy.

Gastroenterologists are rightly raising questions about the validity of previously held concepts of the worth of antacids, diet, and anticholinergics in treating peptic ulcer. But I suspect that until convincing data are presented, many would not feel comfortable with Piper's conclusion that ". . . intensive antacid therapy has no place in the treatment of peptic ulcer." Until hard, convincing data are available it seems more appropriate to be in the position of an agnostic, while always eager to adopt anything new of proven superiority over the old.

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Cirrhosis with Portal Thrombosis*

A Difficult Problem

THE PHYSICIAN or surgeon, confronted with a patient whose cirrhosis and portal hypertension is complicated by occlusion of the portal vein, needs no reminder of the dilemma created by this unfortunate combination. The problem is clearly presented in the report by Sicot and colleagues[1] which appeared in a recent issue of this journal. In their review of 250 patients who underwent portal-systemic shunt surgery, intrahepatic block was complicated by portal-vein thrombosis in 13 instances. Although the incidence of portal thrombosis that accompanies cirrhosis cannot be determined precisely, the figure probably is 5 to 10%, depending on whether data were collected at surgery or at autopsy. The development of this complication causes further diversion of portal blood from a liver that is already deprived and may aggravate formation of ascites. With the exception of invasion by hepatoma, the cause of portal thrombosis in patients with intrahepatic block is uncertain; but, presumably, reduction in the rate of portal flow is an important contributing factor. The recent demonstration by direct measurement of the severity of reduction of portal flow in cirrhosis[2] lends credence to this hypothesis. Also, changes in the wall of the portal vein may occur in cirrhosis[3] and could provide a focus for thrombus formation.

The tendency of portal thrombosis to develop after splenectomy is well recognized. This sequence is supported by the observation of Sicot et al. that portal occlusion was attributable to prior splenectomy in six of 13 instances. The inadvisability of splenectomy alone in the patient with portal hypertension is thus emphasized, because, in addition to risking portal thrombosis, one eliminates the most convenient means of access to the portal system for future portography and usually precludes use of the splenic vein for a surgical shunt.

Although portal occlusion reduces the likelihood of a successful shunt operation, demonstration of a definite portal block by splenoportography is of considerable assistance to the surgeon who is considering portal-systemic anastomosis. As pointed out by the authors[1], nonopacification

*Sicot, C., Sakellaridis, D., Rueff, B., Maillard, J.-N., and Benhamou, J.-P: Portal Vein Thrombosis in Intrahepatic Block. Minnesota Med 54:87, 1971.

of the portal trunk should not be construed as certain evidence of portal occlusion because the portal vein is, in fact, patent in most such instances. Failure to opacify the portal vein is probably caused by diversion of contrast medium via extensive portal collaterals, stagnation (or even reversal) of portal flow, or streaming of blood in the portal vein. In such instances, the status of the portal vein often can be clarified by mesenteric portography, which can be performed through a small abdominal incision preliminary to shunt surgery. The principal hope for the patient with cirrhosis and extrahepatic occlusion is the roentgenographic demonstration of a mesenteric vein sufficiently large to allow construction of a caval-mesenteric shunt. Although these lesser shunts often function well, the likelihood of thrombosis of the shunt and rebleeding from varices is high.

Finally, the difficulties presented by portal occlusion in cirrhosis are exemplified by Adson's experience with emergency shunt procedures.[4] Of the eight deaths among 30 patients, six occurred in those with preexisting extrahepatic portal thrombosis, thus emphasizing the problem created by this complication in situations in which preliminary roentgenographic evaluation of the portal system may be less than optimal.

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Minnesota Medicine Editors

Hidden under the facade of the practicing physician must lie in some the frustrated desire for a career as a writing man. Doctors, members of the Minnesota State Medical Association, have been known to write plays, magazine articles, and books even to the best seller list.

MINNESOTA MEDICINE needs the help of members who write and members who would like to do some editing of what others write. The Board of Editors would like to hear from any member desiring to join the Board, indulging themselves in some writing for the journal, and taking on the responsibility for editing a few manuscripts each year. Anyone interested in being considered for the Board is asked to communicate with Dr. Richard Reece, St. Barnabas Hospital, Minneapolis 55404.

Cover Photo

"The Greenhouse"

Dr. Edward A. Banner, Mayo Clinic obstetrician-gynecologist, states that the inspiration for his painting the beautiful cover for this issue came about by visiting a greenhouse, the Holm & Olson Greenhouse, in Rochester. "The soft texture and brilliant colors of the numerous flowers seemed exhanced by the three dimensional architecture. It was this latter quality which I tried to emulate in my painting," says Dr. Banner.

Besides painting as a hobby, Dr. Banner flies planes and drives sports cars.

Editor's Soliloquy

Twenty-First Century Medicine on the Kitchen Table

I ABHOR THE bureaucratese that orates in multifarious and meaningless phrases: "medical care distribution," "health manpower utilization," "patient care delivery," and the thousand and one other ear-appealing but denigrating terms designed to produce an unfavorable image of the system under attack, as if medical care were inaccessible or unavailable.

As with any other Twentieth Century product or service, it should be recognized as basic, that modern advanced medical service can be dispensed only after an accurate evaluation and diagnosis are made and only from the physician's office, the clinic, or the hospital where medical care can be administered scientifically and accurately. Only primitive medical service can be dispensed in the farmyard, on the kitchen table, or in the remote sections of the country: in the woods of the Northwest Angle, in the hills of the Blue Ridge, or in a Toonerville.

For decades we have been advising our patients to get themselves into optimum physical condition and function with a bit of calorie control, moderate exercise, and sensible living patterns. Too many of them take no heed, but insist upon receiving a magic pill, a health-restoring shot, an all-inclusive test and a clairvoyant film diagnosis, as if we were tireless, infallible robots, endowed, like the Creator, with omniscience and omnipotence. Malnutrition in the corpulent, lack of physical trim in the undisciplined, filth in the unwashed, and emotional exhaustion in the hypochondriac are the major causes for illness. Control of these is within the reach of the patient alone.

There is no serious dearth of ambulatory care if the patient will walk from his car to the doctor's office to receive it. We have the best medical system on the planet, and to decry it on the basis of infant mortality or any other insular statistic is grossly misleading.*

In contradistinction to the politicians, the do-gooders, the social reformers and their spokesmen, who initiate the major criticisms of the medical profession, our medical science has already advanced into the Twenty-First Century.

If it is true that only twenty percent of the population are without some kind of health insurance,† then it is obvious that there is no acute massive crisis in health care.

If there is nothing greater than the "dreariness" of consulting the physician that keeps people away from the doctor's office, as Lewis has indicated, that fact can hardly reflect a paucity of medical care, but only a natural propensity to disregard a service that ordinarily is not desired unless definitely needed.

It appears to me that too many of our complainers want Twenty-First Century medicine on the kitchen table.

—Carl O. Rice, M.D.

*Albert Q. Maisel, National Health Insurance, Reader's Digest, Feb. 1971.
†Irving J. Lewis, Scientific American, April 1971, page 17.

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Thrombus Formation on Polymeric Materials

IV. Behavior of Blood Proteins at Interfaces

DOUGLAS A. OLSEN, Ph.D.,* HAROLD D. KLETSCHKA, M.D.† and JAMES LEROY HAYNES, M.S.*

THE DISCUSSION of the previous articles‡ gave the classical mechanism of blood clotting with minimal reference to thrombus formation on surfaces. The various blood clotting factors are proteins; thus it would appear that to understand thrombus formation on surfaces, the adsorption of proteins on surfaces must be more fully understood. It also appears that clotting on surfaces proceeds via the intrinsic pathway.

Protein Properties and Adsorption

Most proteins that we are dealing with are so large and flexible that the first and foremost interfaces they must come in contact with are their own and those of one another. This subject, as it pertains to blood coagulation, has been reviewed in detail by Vroman.[1] In solution, the single globular protein molecule must be expected to look like a tangled helix, of which the helical character depends mostly on hydrogen bonding along the backbone and the tangled character more than on hydrophobic groups between the irregularly-placed amino acid residues. These nonpolar groups will protect each other from the surrounding water and will find their optimally stable location in the heart of the tangle, with the more polar amino acid groups arranged around them.

Both types of sites are important in blood coagulation. A consequence of hydrophobic sites on proteins is the ability of lipoproteins to bind lipids.[2] More important to blood coagulation is the contribution that hydrophobic bonds[3] have on the shape (conformation) of enzyme molecules, thereby affecting the availability of specific reactive enzyme sites.

Proteins at Interfaces

At an air-aqueous interface, globular proteins will "turn inside out,"[4] spread at the interface with hydrophobic groups pointing to the air and hydrophilic ones to the water, and press the surface water down into the bulk water. The hydrophobic surface of the protein has then replaced the less "hydrophobic" surface water. Implicit in these statements is the possibility of a systematic error in many blood clotting determinations. Any time blood has been exposed to an air interface it is probable that at least a monolayer of protein has changed its conformation. Such monolayers may be transferred to the surface being examined and thus produce spurious results. Statements recognizing this effect do not generally appear in the literature.

At solid interfaces, as well as in bulk, proteins have been shown by infrared spectroscopy to displace water.[5,6] The amount of water displaced is specific, depending on the hydrophobic internal area of particular protein molecules. Thus it appears that a conformation change occurs as for air-aqueous interfaces.

At interfaces, adsorbed proteins affect wettability.[7,8] Adsorbed films of proteins, such as thrombin and fibrinogen, decrease the wettability of glass surfaces, but increase that of polymethylmethacrylate.[9] The proteins cannot be easily removed.[10] This indicates that hydrogen bonds are involved as well as hydrophobic

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‡See page 773 of July issue, page 877 of the August issue, and page 989 of the September issue, 1970.

bonding.[11] Protein adsorbed onto paraffin is held only by hydrophobic bonds and is easily lifted off.

Surface charge is also affected by protein adsorption as shown by zeta potential[12] and electrophoretic behavior.[13] A polymer, for example, will find its surface charge not only neutralized but reversed when it adsorbs an excess of albumin, so that it appears coated with a layer of protein that has the same electrophoretic mobility as bulk protein.[13] A wide variety of surfaces has been shown to adsorb proteins from plasma; and widely-diverse zeta potentials will converge in the process,[14] without correlating with clotting times in contact with these surfaces.

The foregoing investigations implicate surface charge and surface energy as factors which affect the adsorption of proteins on surface. In a mathematical study, Levine[15] has derived expressions relating these quantities to the binding constants of the proteins. Only monolayer adsorption is dealt with, and the results cannot yet be applied to practical systems.

In summary, it seems that any protein will probably be adsorbed onto any surface to some degree. Its conformation will always be affected so that its ability to act as a substrate or enzyme at the interface will be either decreased or increased by the adsorption, depending on the adsorbent.

When specific interactions between blood proteins and surfaces are considered, the available literature falls into two main classes, viz., where the emphasis proceeds either from a protein or from a surface point of view. We shall review the former first.

Behavior of Blood Proteins on Surfaces

Considerable study has been carried out relating to the effect of foreign surfaces on specific proteins of the blood. For example, a number of defects of the coagulation mechanism have followed cardiopulmonary bypass, which were the result of changes incurred involving the role of specific proteins in the clotting scheme. Hypofibrinoginemia has been recorded as a frequent occurrence;[16-21] in addition, hypoprothrombinemia has been recorded[20,22] as well as diminished levels of Factor V[20] and Factor VIII.[23,24]

Protein Adsorption

Protein adsorption with possible lipid deposition occurs rapidly when a surface is placed in contact with blood.[25-27] Mirkovitch et al.[14] showed that a wide variety of surfaces adsorb protein from plasma. Vroman[1] found that all protein-containing solutes showed adsorption onto the various surfaces tested at an initial rate of about 10-20 Å per minute. This rate decreased gradually for plasma and other complex mixtures, and more abruptly for more purified proteins (such as Factor XII, prothrombin, thrombin, cytochrome c, hemoglobin A, and insulin). Adsorption was followed by desorption only where intact Factors XI and XII were both present. Vroman's experiments showed that the rate and amount of antiserum adsorbed onto films formed by plasma indicate that about two thirds of those films consisted of fibrinogen and also that fibrinogen may be a major component involved in the normal adsorption and desorption process.

The Hageman Factor

Factor XII, the Hageman factor, obtained from various sources, has been purified and characterized.[28-30] Activated Factor XII is described as a gamma-globulin with a molecular weight of 80,000 ± 20,000. Prior to 1960, the existence of Factor XII was still doubted by many.[1] There is little available information on its adsorption by surfaces, although the discussion of the waterfall sequence assumes that contact with a surface activates the factor.[31] Heparin does not inhibit surface activation of Factor XII, probably because, with its negative net charge, it will be adsorbed onto the surface only after Factor XII has been adsorbed and has rendered the surface more positive. Aluminum oxide, which can be given either sign of surface charge, will activate Factor XII only when negative. The ability of sodium urate to activate Factor XII has also been attributed to its negative charge. The shape of the Factor XII molecule probably changes when it is adsorbed.[1] Optimal activation by quartz occurs at a particle size near, but not smaller than, the expected size of the Factor XII molecule. Apparently the curvature of

the surface distorts the protein maximally under these conditions. Bentonite crystals, on the other hand, are flat and would, therefore, be optimally active at larger diameters.[32] The distortion is thought to expose active groups otherwise hidden, a process suggested to be reversible. The activity of Factor XII is postulated to be initiated by contact of blood with foreign surfaces, of which glass is one of the most active.[33]

Heparin Action

O'Brien[34,35] hypothesizes that heparin in solution is reversibly complexed with Factor IX, and this hypothesis has been extended by Merrill et al.[36] to include heparin irreversibly bonded to a solid substrate in such a way as to have a portion of the active sites of heparin exposed to the contacting solution. Thus the adsorbed heparin layer may adsorb one or more intrinsic clotting factors without causing their denaturation and, when finally saturated with these undenatured plasma components, may become a passive surface.

Denaturation of Thromboplastic Factors

Reductions have been noted in all thromboplastic factors during and following cardiopulmonary bypass.[19,23,37-39] More recently, Porter and Silver[40] carried out studies in patients undergoing open heart surgery with cardiopulmonary bypass, and a rapid and significant decrease in both prothrombin and Factor V activity occurred shortly after the onset of bypass. Factor VII activity decreased only slightly, while fibrinogen decreased to 50 percent of the preoperative levels. These investigators noted that the labile thromboplastic factors, such as V and VIII, undergo the greatest reduction on bypass, while the stable factors, such as VII show little or no reduction. One of the possible causes for the observed changes, they postulated, could be due to protein denaturation by surface contact in the pump. Lee et al.[41] also reported similar findings. Attar,[40] in commenting on the work of Porter and Silver, pointed out results on a patient population similar to that of Porter and Silver, and found that deficiencies of clotting factors included not only the extrinsic prothrombin activator system reflected by changes in prothrombin, Factor V and VII, but also the intrinsic prothrombin activator system which includes Factors VIII, IX, XI and XII. His group further noted that the increased fibrinolytic activity produces undesirable effects through the degradation products of fibrinogen which acts as antithrombin and induces defective fibrin polymerization. The half-life of those products was noted to be about nine to 10 hours.

Surface Activity of Specific Factors

Factors V and VIII are not readily adsorbed by many hydrophilic surfaces.[42] Celite will adsorb phospholipid in such a way that the lipid removes Factor V most efficiently from solution,[42] probably by arranging the molecules with the apolar tails exposed to the medium. When adsorbed onto various insoluble soaps, human Factor V shows no activity, but bovine Factor V remains active when adsorbed onto barium stearate.[12] Bovine Factor V appeared only temporarily inactive when bound to polystyrene latex;[43] when adsorbed on phospholipid micelle, the activity of bovine Factor V depends on the nature and amount of interface available.[44] The inhibitory effect of many hydrophobic interfaces, especially on human plasma, might be a result of Factor V, Factor VIII, and thrombin being adsorbed at unfavorable sites.[1]

Purified prothrombin, added to prothrombin-poor plasma, is poorly converted to thrombin in siliconized glass test tubes, but converted well in plain glass. Glass does adsorb prothrombin,[45] so that thrombin may form at a glass surface. Prothrombin, when adsorbed onto hydrophilic surfaces, seems to be more available for conversion to thrombin than is prothrombin adsorbed onto hydrophobic surfaces. Purified prothrombin, for example, has been adsorbed onto barium sulfate and then converted to thrombin by exposing the washed powder to protamine sulfate. However, the same manipulations with barium stearate (a quite hydrophobic powder), as the adsorbing agent, did not yield measurable amounts of thrombin.[46] Thrombin is adsorbed more readily onto barium stearate than onto barium sulfate (thus behaving oppositely to prothrombin), but is less active on the stearate. Also thrombin, adsorbed onto wettable tantalum oxide surfaces, adsorbed more fibrinogen than did

thrombin adsorbed onto tantalum oxide surfaces made hydrophobic with fatty acid.[25] These findings may be explained by assuming that prothrombin is a coil with its more hydrophilic amino acid residues at its surface. When its outer portion is removed or opened by adsorption, the remaining protein has a higher percentage of hydrophobic amino acid residues and has the ability to expose these as well as its thrombin activity.[1]

Fibrinogen is readily adsorbed by certain hydrophobic surfaces. Adsorption onto the surface areas of test tubes, from plasma that contains large amounts of this protein, should affect subsequent coagulation rates in the tube. However, the normally close association between fibrinogen and Factor VIII, both apparently having hydrophobic sites readily available, may be affected by competing interfaces. The activity of one might also be affected where the other is absent. Blomback et al.,[47] for example, found that the sedimentation rate of fibrinogen, isolated from Factor VIII-deficient plasma, increases with concentration, while under normal circumstances, it does not. Possibly, fibrinogen that contains little Factor VIII will form dimers or larger complexes instead.[1]

Heparinized Surfaces

Studying protein adsorption on heparin-modified cellulose membranes, Merrill et al.[36] noted that heparinized surfaces strongly adsorb plasma components. In this study, they used tritium-labelled plasma proteins. The total amount of adsorbed plasma components was found to be very nearly equal to the weight of heparin adsorbed per square centimeter. The adsorption of protein onto the heparin surface levelled off after 30 minutes of vigorous agitation, indicating a saturation of the surface at that point with the plasma proteins. Merrill and associates demonstrated that calcium ion is not significantly involved in the bonding of the plasma proteins to the heparinized surface. It was found in their experiments that cellulose, silicone rubber, and cellulose imine surfaces all adsorb plasma proteins, but to a lesser degree than the corresponding heparinized surface. Additional observations were made by these experimenters, showing that no heparin was desorbed from the graphite-benzalkonium-heparin surface into isotonic saline under any conditions of fluid shear, but that heparin was progressively released when in contact with blood plasma, and that the rate of release was a strong function of the fluid shear stress. This was interpreted by the authors to mean that the plasma proteins adsorb on the graphite part of the graphite-benzalkonium-heparin surface in such a way that they break the physical sorption of the hydrocarbon moiety of the benzalkonium chloride on the graphite. They felt that proteins can strongly adsorb on nonpolar surfaces such as graphite and silicone rubber. For the latter surfaces they noted a very strong and immediate adsorption of plasma proteins quickly rendering the surfaces hydrophilic.

Falb et al. [48] demonstrated that both heparinized and unheparinized surfaces rapidly adsorb proteins when placed in contact with blood or plasma; surfaces in contact with blood are strongly modified by the adsorbed protein layer. The purpose of the experiments summarized in Table 1 was to examine differences in the adsorptive properties of unheparinized and heparinized surfaces and thus obtain information as to the mechanism by which heparin-bearing surfaces are rendered non-

TABLE 1

Adsorption of Plasma Proteins on Surfaces[48]

Protein solution (at physiological concentration)	Mg proteins adsorbed x 10^3/cm^2		
	Styrene-grafted polypropylene	Quaternized polypropylene	Heparinized polypropylene
Plasma*	48.3	7.5	8.3
Albumin	3.0	6.6	2.8
γ-Globulin	19.3	22.4	21.4
Factor XII	4.3	53.8	14.8
Thrombin	0.62	2.5	4.3

*The results of the plasma adsorption study are difficult to interpret because of the non-uniform labeling of the various proteins, and the possible preferential adsorption of less strongly labeled proteins.

thrombogenic.[48] It has been stated by several authors[49,50] that the reason for the nonthrombogenicity of heparinized surfaces (and the vascular intima itself) is that these surfaces are negatively-charged and thus repel negatively charged proteins. The data in Table 1 do not bear out this supposition. It can be seen that, with the exception of Factor XII, not much difference can be found in the amounts of proteins adsorbed by the positively-charged quaternary ammonium salt surfaces and the negatively charged heparinized surfaces.

The adsorption characteristics of Factor XII are of particular interest, because it is believed that the first step in surface-induced coagulation is the adsorption of Factor XII. The results from this study show that Factor XII was adsorbed much more strongly by the positively-charged quaternary ammonium surface than by the negatively-charged polypropylene and heparinized surfaces. It should be noted, however, that the nonthrombogenic heparinized surfaces adsorbed Factor XII more strongly than did the thrombogenic polypropylene surfaces, indicating that heparinized surfaces do not owe their nonthrombogenicity to a reduced adsorption of Factor XII. It is conceivable, however, that Factor XII adsorbed onto a heparinized surface is functionally different from Factor XII bound to an untreated surface. Such functional differences could result from different modes of binding of Factor XII to charged and uncharged surfaces.

The data of Table 1 on the adsorption of thrombin onto the test surfaces may shed some light on a possible mechanism involved in the nonthrombogenic characteristics of heparinized surfaces. The data show that seven times as much thrombin was adsorbed by the heparinized surface than by the styrene-graft polypropylene surface. This may be significant, because one of the reasons given for the anticoagulant activity of heparin is the formation of a heparin-thrombin complex.[48]

If the adsorption and subsequent inactivation of thrombin were the sole mechanism responsible for the nonthrombogenicity of heparinized surfaces, it would then appear that these surfaces would have a limited lifetime due to an eventual complete coverage of the surface with thrombin. However, Gott et al.[51] point out that while heparin blocks the conversion of prothrombin to thrombin and similarly blocks the conversion by thrombin of fibrinogen to fibrin, it also blocks the agglutination of platelets, which is likewise enhanced by increased amounts of thrombin and fibrin. They believe wall-bonded heparin acts in a similar manner to prevent thrombosis. Nevertheless, they feel that even more important than the foregoing blocking mechanisms of heparin is the possibility that, as a wall-bonded anticoagulant, it interferes in some way with adsorption and denaturization of important clotting proteins such as Factor XII.

Variation of Surface Functional Groups

In other work, Oja et al.[52] studied the adsorption of the various coagulation factors onto surfaces with varying functional groups. Well-washed cellulose served as a control and had little effect on the activity of Factors I through XII. Cationic (quaternary amine)-modified cellulose caused reduction of Factors II, IX, and X. Heparinization of these surfaces resulted in a consistent reduction of Factor IX only. Contact of plasma with surfaces bearing strongly anionic (sulfate, sulfonate) and weakly anionic (carboxylate) surfaces showed no clearly consistent pattern. In particular, Oja found no significant adsorption of Factor XII by either cationic or anionic surfaces in contrast to the findings of Falb et al.[48,53]

Surface Properties and Coagulation

Recent studies have proceeded from the point of view of varying the nature of the surface while studying coagulation. As noted above, adsorption occurs on the contacting surface (though the substance is not necessarily the same for each surface); this, in turn, either directly or indirectly activates the clotting reaction. For example, Margolis[32] showed that colloidal silica adsorbs and partially denatures a specific plasma protein (Factor XII) and the activity of silica depends on the protein-particle geometry. It would appear, therefore, that one not only must consider the surface of the polymer per se but also must define the chemical nature of the surface which would range from neutral, negatively or positively-charged func-

tional groups in the polymer to an adsorbed monolayer. All these diverse quantities may be represented by one integrated quantity, the surface-free energy of a solid.

Surface-Free Energy and Coagulation

The surface-free energy of a material is available to provide the interaction energy required to induce coagulation in the blood-polymer system. This energy may be increased by the presence of specific ultra-high energy sites at lattice defects in crystals, faces, edges, or strain points in the material. The presence of impurities (such as catalyst residues) or additives (such as antioxidants or stabilizers) can also add to the surface-free energy of the polymer surface. The point in the coagulation process where this energy is utilized to initiate or induce clotting is also dependent in part on the chemical structure of the surface which influences the nature of the substance being adsorbed.

The specific surface-free energy of solids ranges from a high of 5000-500 ergs/cm^2 for materials such as silica, inorganic salts, diamond, and metals to 100-25 ergs/cm^2 for waxes and organic polymers to as low as 5 ergs/cm^2 for certain oriented organic monolayers.[54] Lyman et al.[55,56] showed that on a semilogarithmic plot, the surface-free energy versus *in-vitro* coagulation time for human blood has a linear relationship. Similar plots for both *in-vitro* and *in-vivo* coagulation of dog blood again give a good linear relationship between surface-free energy and coagulation time. These observations were qualified since only hydrophobic materials were used. Most commercially-available polymers are of this type. On the other hand, the authors noted that the vascular walls are hydrophilic in nature, and that further studies with hydrophilic polymers would be necessary in order to determine whether the initial observations they made could also be applied to this class of polymers.

Baier et al.[57] have stated that two well-recognized processes may be occurring here: (1) the adsorption of proteins leading to coagulation; and (2) the adhesion of platelets, at first to the solid and then to each other. The growing mass of platelets forms a thrombus which adheres to the solid surface. Surface attraction of the solid is involved in three ways: (1) in the adsorption of proteins; (2) in the initial adhesion of the platelets; and (3) to some extent in control of the adhesional lifetime of the thrombus. The lifetime (and therefore the aggregate size) of the thrombus should decrease with decreasing surface-free energy of the foreign surface because of the poorer adhesion to lower-energy surfaces. Consequently, the smaller size of the thrombus upon detachment from such a surface should result in a decreased likelihood of embolism downstream.

The surface-free energy of polymers has received considerable attention in the past decade. Much of the work has been carried out by Zisman and his co-workers[54] who have developed the concept of the critical surface tension, which is an excellent estimate of the surface-free energy, the latter quantity being difficult to measure. As noted, clotting behavior is related to the surface energy which in turn can be related to molecular constitution. One approach is that of Wu,[58] where the critical surface tension is shown to be related to the cohesive energy density which can be determined from a knowledge of the molecular structure. An obvious goal is to predict the molecular structure necessary to give a surface that would not induce the coagulation of blood. At present, this approach is restricted to materials which are relatively hydrophobic and whose adsorption characteristics might be somewhat similar.

TABLE 2
Thickness of Adsorbed Protein Films[56]

	Thickness of Adsorbed Protein (Å)			
Protein	Polystyrene	Polyethylene	Polydimethyl-siloxane	Teflon FEP
Albumin	44	62	120	62
Gamma-Globulin	54	77	138	0
Fibrinogen	130	96	120	108

Monolayer Adsorption of Proteins

Lyman et al.[55,56,59] have also adsorbed monolayers of albumin, globulin, and fibrinogen onto several polymers. They studied each protein-polymer system by determining the quantity of protein adsorbed as a function of solution concentration, and found that a plateau of adsorbed layer concentration is apparently reached at solution concentrations of about 5 to 7 mg percent. This does not change appreciably with increase in protein concentration to about 20 mg percent and, in some cases, up to normal plasma concentration. The calculated layer thicknesses are summarized in Table 2. In all cases, the thickness of the monolayer was greater than 44 Å. A spread, and consequently denatured, monolayer would average perhaps 10 Å in thickness. The monolayer was deduced to be a closely-packed array in which the protein molecules appeared to retain their native globular form and were adsorbed more or less end-on to the surface.

The adsorption was not reversible. The proteins were not desorbed over a wide range of pH, nor were they removed even by extensive ultrasonic vibration. Lyman et al.[56,59,60] concluded that plasma proteins are strongly adsorbed to hydrophobic polymer surfaces and that drastic dimensional changes usually associated with surface denaturation do not occur. This behavior is in marked contrast to the uncoiling and spreading of proteins observed at air/water interfaces. If it is assumed that all the plasma proteins are similar in their adsorption properties, their data implied that polymer surface-induced blood coagulation may not be initiated by the postulated contact, adsorption, denaturation-activation sequence of Factor XII at the surface. It should be noted that Teflon FEP exhibited a selective protein adsorption. While it adsorbed albumin and fibrinogen in quantities comparable to the other surfaces studied, it did not adsorb gamma-globulin. Lyman and associates found this difficult to understand since these proteins differ only in size and not to any marked degree in the type of structure that is presented to the polymer surface.

Surface-Free Energy and Platelet Adhesion

Lyman, Brash, and co-workers[60,61] discovered that there is a direct link between the amount of blood platelet adsorption on a polymer surface on the one hand, and the surface-free energy of the polymer on the other. They theorize that blood platelet adsorption is a primary requirement for clotting. Once adsorbed, disruption of the platelets or their degradation may then trigger activation of Factor XII. On the other hand, they may initiate clotting in a manner similar to that shown by damaged vascular lining where the combination of platelets and tissue products tends to short-circuit the overall cascade scheme and react directly in the later events of the scheme leading to formation of the fibrin clot.

Lyman and Brash[61] also found that platelet adsorption on polymer surfaces is effectively reduced to zero when these surfaces are precoated with albumin and other blood proteins. These results seem to be contradicted by Baier, Dutton et al.[62,63] who found that platelets did not adhere directly to foreign surfaces, but instead required a film of blood protein preliminary to platelet adhesion. Mason et al.[64] point out that the presence of a blood-air interface increases the tendency of platelets to adhere to polymers; they attribute this to a layer of denatured protein deposited from the blood-air interface.

Summary

The nature of the blood protein-polymer interactions are exceedingly complex and far from being understood. Once the interactions are known, new methods of preparing nonthrombogenic surfaces should become apparent. As will be discussed in the next article, damage to the formed elements is an interrelated problem.

References may be secured from the author or the reprints.

Nature knows no pause in progress and development, and attaches her curse on all inaction.—Goethe

Historic Hospitals

The Suppression and Refoundation of St. Bartholomew's Hospital



St. Bartholomew's Hospital in 1720 with the King Henry VIII Gateway. Courtesy National Library of Medicine, Bethesda, Maryland.

Responsibility for the care of the sick poor began to shift gradually from the Church to secular bodies, usually municipalities, in the late Middle Ages. In England the shift was precipitous, brought on by the struggle between Henry VIII and Rome which ended with the king declaring himself Supreme Head of the English Church. The systematic extinction of the monasteries ordered by Henry extended to the hospitals and, by 1539, 110 hospitals had been suppressed and their revenues seized.

A desperate situation resulted, particularly in the cities, where the sick lay begging in the streets. The Lord Mayor of London petitioned the king in 1538 that the three remaining hospitals in the city, St. Bartholomew's, St. Mary Spital, and St. Thomas's be placed with their revenues at the disposal of the Mayor and aldermen, so that "all impotent persons not able to labor might be relieved." Six years elapsed before Henry finally replied, decreeing that St. Bartholomew's Hospital be named after himself, and providing an annual endowment of 500 marks. The citizens of London repaired the hospital at their own expense and provided another 500 marks annually so that it could be opened for one hundred patients.

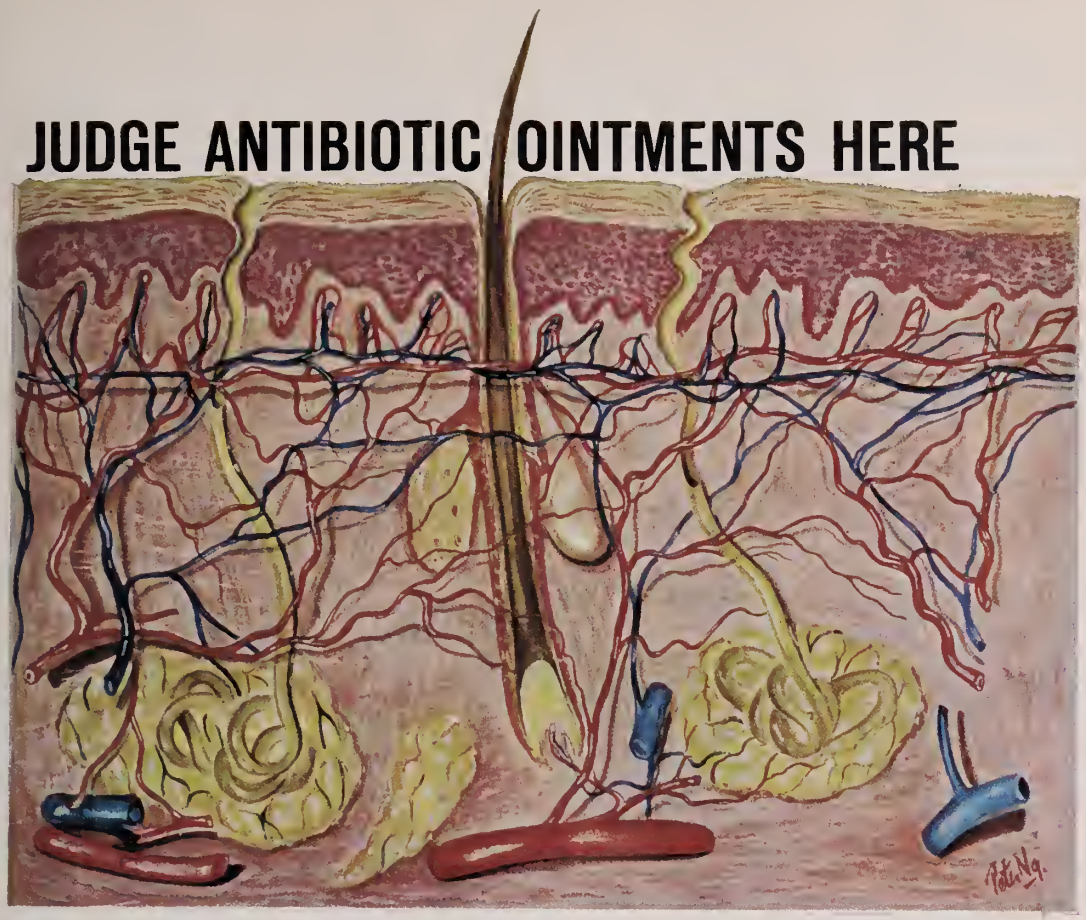
Still the king withheld the hospital's properties and failed to provide adequate support. His physicians predicted that he would continue to do so until he himself fell ill. Their prediction proved correct when, on his deathbed in 1547, he returned the hospital's properties and made the comprehensive agreement with the citizens which led to his posthumous, if unmerited, distinction as founder of the five "Royal Hospitals", including St. Bartholomew's.

Although it was through the efforts of the citizens that the hospital was preserved, Henry has received some recognition for its "refoundation." The entry to the hospital shown in the above engraving made in 1720 is known as the King Henry VIII Gateway. It was built in 1702 and includes a statue of Henry and the Royal Arms.

Warren L. Kump, M.D.
Minneapolis, Minnesota

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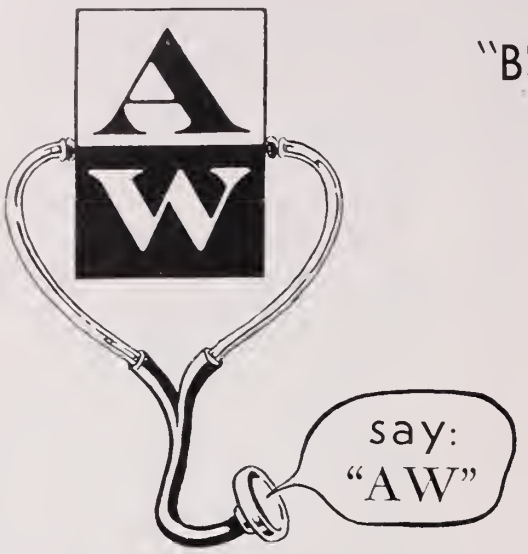
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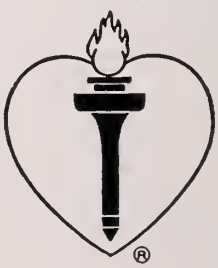
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Case Report

Terpenes in the Treatment of Gallstones

B. Z. HORDINSKY, M.D.*

No theory of gallstone formation, other than for the bile pigment stones associated with hemolytic anemia, has stood the test of time and scientific inquiry. Recently new concepts regarding the etiology of cholesterol gallstones have been introduced. In 1954 Isakkson concluded after detailed analyses of human bile that the amount of bile salts was not sufficient to hold all the cholesterol in solution.

Roche scientists, believing that gallstones can be dissolved and surgery avoided, have investigated a number of solvent agents. P. L. Stefko,[3] a member of the Roche group, describes the rationale for the research this way: "The initial step (in the etiology of gallstones) is the precipitation of biliary cholesterol deposition, more cholesterol or other materials deposit, to form various types of stones."—"If with a drug, one can increase the bile flow (cut down viscosity of bile), the drug could possibly facilitate fragmentation and disintegration of stones—drawing cholesterol out of it so it could dissolve and pass down the tract."

Two of the Roche compounds found to cause cholereisis were investigated. By implanting human gallstones in drug-treated dogs, Stefko and associates have been able to observe the effects of these agents on biliary flow and dissolution of the stones. Drugs in this class, they believe, are virtually unlimited in their future accomplishments.

This paper reports observations on patients with gallstones treated with volatile oils, which are strong choleretics.

Volatile or essential oils occur widely in the plants and have been used in medicine for centuries. Chemically volatile oils contain hydrocarbon terpene ($C_{10}H_{16}$) or some polymere of this. The terpenes are excreted by the kidneys, having been esterified in the liver with glucoronic and sulfuric acid and through excretion

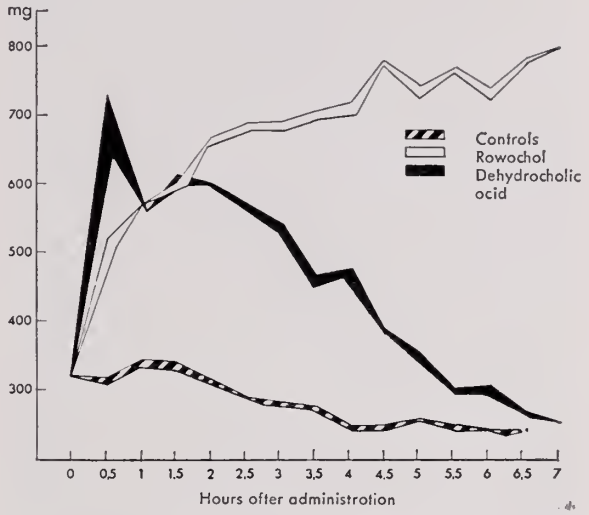


Fig. 1—Volume of bile secreted after administration of Rowachol and of dehydrocholic acid.

(Permission given by Dr. Hans Braun and Duncker & Humblot of Berlin to publish this figure appearing in Dr. Braun's article Zeitschrift für Therapie.)



Figure 2

*Drake, North Dakota
See editorial, page 626.

of the bile. Because volatile oils are strong choleretics they were investigated for their effect on gallstones. We used the following combination of volatile oils in purified form:

Menthol	32%
Menthone	6%
Pinene	17%
Borneol	5%
Camphene	5%
Cineol	2%
Olive oil a.d.	100%

Such a combination was produced by Rowa-Wagner Pharmaceutical Laboratory in Bensberg, Germany, and packaged under the name of Rowachol. Despite its high terpene content, Rowachol is non toxic, as the research of Geinitz and Graeber[1] have proven.

A pharmacological study by Savini of the University of Paris showed that intraduodenal administration of Rowachol to rats resulted in a prolonged and significant increase in bile secretion. Similar results,[2] comparing the volume of bile secreted after dehydrocholic acid and after Rowachol, showed that dehydrocholic acid produced a larger amount of bile, for a shorter period of time; the production of bile after Rowachol was much more prolonged.

One hundred and fifty-one patients with gallstones were treated with Rowachol. Each patient received two drops four times a day. Each had an x-ray of the gallbladder before treatment and every three months during the treatment period. Each patient also had weekly a complete blood count, a urinalysis, an alkaline phosphatase, a S.G.O. and a S.G.P. transaminase.

Case Reports

Case No. 1

A 44-year-old woman had many gallstone attacks; an x-ray showed one large stone (Figure 2). After three months of treatment with Rowachol the gallstone looked different and was almost disintegrated (Figure 3). Three months later the x-ray was negative (Figure 4).

Case No. 2

A 71-year-old woman had many gallstone attacks; an x-ray revealed many stones (Figure 5). After three months of treatment the x-ray showed none (Figure 6).

Case No. 3

A 33-year-old woman had many stones (Figure 7). After three months' treatment the x-ray was negative (Figure 8).

Case No. 4

A 40-year-old woman had a history of many gallstone attacks; an x-ray showed many stones (Figure 9). Three months after treatment the x-ray was negative (Figure 10).



Figure 3



Figure 4



Figure 5



Figure 6



Figure 7



Figure 8



Figure 9



Figure 10

One hundred forty-seven patients did not show any change in the size of gallstones after three and after six months. There was no change in liver, blood and urine tests in all 151 patients.

Summary

This paper presents four patients who had gallstones that were apparently dissolved by taking volatile oils in the form of preparation Rowachol. No patient showed any damage to the liver, kidneys, or blood after taking volatile oils for three to six months.

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Proper Dress

Women who already look like fat, waddling walruses should abhor fur coats and mink stoles, for they add to the elephantine profile. Even a hippopotamus doesn't add thick fur to his bulging sides.*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

In Memoriam

ARTHUR N. COLLINS, M.D.

Dr. Arthur N. Collins, 94, retired Duluth surgeon, died December 19. Born in Dubuque, Iowa, Dr. Collins graduated from the University of Minnesota and the Harvard University Medical School. Prior to his coming to Duluth in 1912, he served at the Mayo Clinic in Rochester.

Dr. Collins was past president of the Mayo Clinic Alumni Association, St. Louis County Medical Society, Northern Minnesota Medical Association and both the Soo Line and Great Northern Surgical Association. He was also a past vice president of the Minnesota State Medical Association and a member of the Duluth Surgical Society, the Western Surgeon's Association, American Board of Surgery and American Medical Association. In addition, he was a fellow of the American College of Surgeons, and a Life and 50 Club member of the Minnesota State Medical Association.

His wife, a daughter, and two sons survive him.

ROBERT N. BARR, M.D.

Dr. Robert N. Barr, 68, Executive Officer of the State Board of Health, died December 26. A University of Minnesota Medical School graduate, Dr. Barr practiced medicine in Montana for three yeare before joining the State Board of Health Department as an epidemiologist in 1934.

In 1964 he received the Minnesota State Medical Association Distinguished Service Award and in his lifetime was a member of some thirty-two various medical societies and associations.

Dr. Barr is survived by his wife, Dr. Lucy H. Barr, and a daughter.

ANDREW SINAMARK, M.D.

Dr. Andrew Sinamark, 82, resident of Hibbing for 50 years, died April 16. Born in Freemont, Nebraska, he had received his medical degree from the University of Nebraska Medical School and had been associated with the Morseman Clinic in Hibbing since 1925.

He was a member of the American Medical Association and the Range Medical Society and a 50 Club and Life Member of the Minnesota State Medical Association.

Dr. Sinamark is survived by his wife and three daughters.

HENRY LYSNE, M.D.

Dr. Henry Lysne, 87, a charter member of the Minneapolis Fairview Hospital medical staff, died May 13. A graduate of St. Olaf College, Northfield, Dr. Lysne received his medical degree from the University of Minnesota Medical School in 1910.

After serving his internship at Hennepin County General Hospital, Dr. Lysne set up a practice in north Minneapolis. He was assistant city physician for Minneapolis in 1912 and during World War I served in the Army Medical Corps. In 1926 he was elected chief of the Fairview Hospital medical staff.

Dr. Lysne was a member of the American Medical Association, the Hennepin County Medical Society and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife.

EARL J. BRATRUDE, M.D.

Dr. Earl J. Bratrude, 74, St. James physician, died March 11. Born in St. James, Minnesota, Dr. Bratrude obtained his medical degree from the University of Minnesota Medical School.

He was a member of the American Medical Association and the Blue Earth Valley Medical Society and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife.

RUTH I. LUNDBERG, M.D.

Dr. Ruth I. Lundberg, 72, Minneapolis general practitioner for 35 years, died March 20.

She was a member of the American Medical Association, the Hennepin County Medical Society and an Associate Member of the Minnesota State Medical Association.

Dr. Lundberg is survived by a nephew.

HUGO O. ALTNOW, M.D.

Dr. Hugh O. Altnow, 84, of Coral Gables, Florida, and retired physician of the Nicollet Clinic in Minneapolis, died May 7. Born in Arlington, Minnesota, Dr. Altnow received his medical degree from the University of Michigan Medical School.

He was a member of the American Medical Association, the American College of Physicians, Minnesota Pathological Society, and the Hennepin County Medical Society and a 50 Club and Associate Member of the Minnesota State Medical Association.

Dr. Altnow is survived by his wife and daughter.

DONALD G. BOHN, M.D.

Dr. Donald G. Bohn, 50, Minneapolis internist, died May 17. He had retired in 1969 as the Medical Director of the North American Life and Casualty Company and had previously been chief of staff at St. Barnabas Hospital.

Born in Great Bend, North Dakota, and educated at the University of Minnesota Medical School, Dr. Bohn was a member of the American Medical Association and the Hennepin County Medical Society. He was an Associate Member of the Minnesota State Medical Association.

DAVID H. EISENSTADT, M.D.

Dr. David H. Eisenstadt, 72, Minneapolis dermotologist, died June 7. Born in Russia, Dr. Eisenstadt attended the University of Minnesota Medical School, graduating in 1923.

He was a member of the Hennepin County Medical Society, the American Medical Association and an Associate Member of the Minnesota State Medical Association.

Dr. Eisenstadt is survived by his wife and two daughters.

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(Continued to page 676)

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Clinical Path Conference

Idiopathic Thrombocytopenia

ROBERT A. GREEN, M.D., HERBERT F. POLESKY, M.D., and
THOMAS F. MULROONEY, M.D.

Dr. Thomas Mulrooney:*

A 65-year-old woman was admitted to Hennepin County General Hospital because of weakness of the left arm. She had suffered from chronic severe mental illness for almost 40 years. Two years before the present admission she had been hospitalized here because of delusions, and a pneumoencephalogram at that time demonstrated atrophy of the frontal and temporal cerebral lobes. Her illness was variously referred to as "chronic undifferentiated schizophrenia" and "presenile psychosis of Pick." For approximately three years prior to her final admission she had been treated with trifluoperazine (Stelazine), and for about three months she had also received hydroxyzine pamoate (Vistaril) in a dose of 150 mg. daily.

Approximately two months prior to the present admission the patient noted the onset of a rash on her lower extremities which persisted up to this admission. About two days before admission she had awakened in the morning with weakness of her left arm. When this symptom persisted she came to the hospital.

On admission, her temperature was 98.6°; pulse 104 and regular; blood pressure 152/90. There was a left hemiparesis without sensory impairment. Slight weakness of the muscles innervated by the lower division of the left seventh cranial nerve was observed. A Babinski sign was present on the left. Examination of the optic fundi was normal. There were petechiae on the mucosa of the mouth as well as on the skin of the legs, arms, trunk and neck. A large, raised, slightly warm ecchymosis was present over the left ankle. The spleen and lymph nodes were not palpable. The remainder of the physical examination was normal.

Laboratory

Hemoglobin was 9.1 grams percent; white blood count, 6,000 with 84% neutrophils, 15% lymphocytes, 1% monocytes. Platelet count was estimated at less than 10,000. Ivy bleeding time was over 10 minutes; prothrombin time, 12.9 seconds with a control of 11.2 seconds; partial thromboplastin time, 32.1 seconds with a control of 29.4 seconds. Fibrinogen level was 0.3 grams per 100 ml. of blood. Direct and indirect Coombs' tests were negative. The reticulocyte count was 5.5%. Examination of the urine was normal. Serum electrolytes, protein, calcium, alkaline phosphatase, bilirubin, and urea nitrogen were also normal. The blood glucose on admission was 180 mg. per 100 ml. A gram stain of the urine sediment was negative. A roentgenogram of the chest was normal.

Hospital Course

Shortly after admission the patient experienced a major motor seizure beginning in the left hand and spreading throughout the left side of the body before becoming generalized. Following this convulsion she had impaired consciousness, deviation of both eyes toward the right and frank paralysis of the central portion of the left facial nerve. She was treated with anticonvulsants, intravenous corticosteroids and three transfusions of fresh platelets. During the next several hours she became completely comatose with flaccidity and areflexia of all extremities and bilateral Babinski reflexes. Her right pupil became dilated and both pupils became unresponsive to light. About 23 hours after admission a bone marrow aspirate showed adequate numbers of megakaryocytes. The patient's condition rapidly deteriorated and she died one hour later.

Clinical Discussion

Dr. Robert A. Green:*

Weakness

The patient was a 65-year-old female with weakness of the left arm. This

*Staff, Department of Internal Medicine, Hennepin County General Hospital.

immediately suggests some type of cerebral vascular accident as the most likely cause of that finding. Her past health was not particularly pertinent except that she had long-standing mental and emotional problems. She had been on tranquillizing medication for a long period, including trifluoperazine for three years and hydroxyzine pamoate for three months. The rash noted for two months before her admission is not discussed in further detail and one wonders if this was petechial, pruritic, eczematoid, or idiopathic. If it had been petechial, it would have considerable bearing on the present problem. Many patients describe diffuse petechiae as a "rash."

The physical findings were principally those of the left hemiparesis and central involvement of the left seventh cranial nerve. She had petechiae diffusely distributed over her body, on the skin as well as the mucous membranes, and a larger hemorrhage on the left ankle. The lack of splenomegaly and lymphadenopathy may help to exclude in part some problems related to what follows.

Laboratory findings revealed a moderate anemia and evidence of an attempt of the bone marrow to respond to this with a reticulocyte count of 5.5%. Her white count was in the normal range with a slight neutrophilia.

The major finding was a platelet count of 10,000. The Ivy bleeding time of "over 10 minutes" was prolonged significantly beyond the upper range of normal, usually considered to be about six minutes. A prolonged Ivy bleeding time is characteristic of thrombocytopenia.

Other clotting parameters were quite normal. This means that there did not appear to be either a consumption coagulopathy or a systemic hemorrhagic disorder due to lack of plasma clotting factors. In this hospital we are coming to recognize consumption coagulopathy as probably the most common systemic hemorrhagic disorder in our older hospital population. The screening tests done on this patient on admission attest to the alertness of the house staff to this possibility in a patient who came in with a hemorrhagic problem. In her case, however, the only deficiency was in the number of platelets.

The remainder of the laboratory investigation was quite normal, with the exception of a blood sugar of 180, which suggests that this patient was very likely diabetic. The prompt and effective workup for a hemorrhagic diathesis attests to the staff's concern for the truly critical nature of the problem: a neurologic deficit in a patient with a hemorrhagic disease. That their apprehension was justified was indicated by the subsequent course of events with deteriorating neurological complications and eventual death. Her treatment was appropriate for the problems involved.

Purpura

True spontaneous petechiae are usually related primarily to platelet deficiency. Other coagulation defects may produce a variety of other manifestations including ecchymoses and hematomas. This patient had one large area of bleeding on her ankle, but the presence of the petechiae suggested platelet deficincy. The fact of her age is somewhat against a diagnosis of idiopathic thrombocytopenic purpura, which is much more common in children. At her age, one's attention immediately turns to the problem of *drug-induced thrombocytopenia,* which makes the history important. Before discussing this, one might ask about other possible associated diseases; but no evidence was found that she had liver disease, infections, dietary problems or findings suggestive of pernicious anemia, any of which might be associated with thrombocytopenia. This returns us to the

question of drugs and the need to check carefully for a history of drug ingestion, particularly for drugs such as thiazide preparations, phenothiazine compounds, quinidine, sulfonamides, meprobamate and some other antidepressant tranquillizer compounds including imipramine and desipramine. We note that this patient had been on long-term trifluoperazine (Stelazine). Although specific problems related to Stelazine have not, to my knowledge, been reported, phenothiazines can produce a variety of cytopenias, including thrombocytopenia.

Thrombocytopenia

Screening studies should include a platelet count, an Ivy bleeding time, a partial thromboplastin time, a prothrombin time and, in addition to these studies when possible, a fibrinogen level or screening test for fibrinogen. These studies in this patient showed normal results except for the low platelet count. This tended to put the focus on thrombocytopenia as the cause of her problem and to exclude a consumption coagulopathy. Initial studies did not include a bone marrow biopsy, but whether this is auto-immune or drug-induced (idiosyncratic) thrombocytopenia, the marrow is not likely to be helpful since in either case megakaryocytes would probably be present in normal or possibly increased numbers. This is in contrast to situations in which myelosuppressive drugs or chemicals cause marrow injury, in which case megakaryocytes are reduced in number.

Chemical Thrombocytopenic Purpura

This then leaves us with the category of symptomatic thrombocytopenic purpura which includes chemical or *drug injuries of the marrow* on the one hand and *hematopoietic disorders* on the other.

In the former, one type involves drugs which are myelosuppressive, such as the *alkylating agents or antimetabolites;* but we don't have any evidence that she had been treated with any of these compounds. The other type includes certain drugs to which some people tend to be hypersensitive or allergic and which may be responsible for a variety of blood cell injuries.

So far as hematopoietic disorders are concerned, we have no evidence in this patient to suggest that she had acute leukemia, aplastic anemia or hypersplenism. The clinical findings do not suggest thrombotic thrombocytopenic purpura in a patient with neurologic disease and thrombocytopenia.

Drugs can produce any type of cytopenia, with purpura if platelets are affected, hemolytic anemia if red cells are affected, and leukopenia if granulocytes are affected. In all of these, sensitization to a foreign antigen, the drug, is involved, resulting eventually in destruction of cells in the sensitized person.

Drug-induced thrombocytopenias have certain characteristic features. They are not very common, although the number of drugs involved is increasing. *Among the most common of these in current practice are the thiazides.* Another characteristic is that one drug usually affects one type of cell, although more than one type of cell may be involved. Quinidine, for example, may cause both thrombocytopenia and hemolytic anemia. Another common feature is that the drug may be taken for a long period of time before cytopenia develops. The explanation for this is not very obvious, but it has something to do with slow development of antibodies. Recovery from the hematologic disturbance usually occurs upon withdrawal of the drug, if the patient survives the initial insult. It is also characteristic that even when the drug is withdrawn, antibody to the

drug can be demonstrated for long periods of time, and the cell-destroying effect will occur with re-administration of the drug. Finally, in this type of idiosyncratic reaction, it is necessary that the drug be present for the reaction to occur.

Drug Antibody Complex

In 1949 Ackroyd reported on the thrombopenic effect of Sedormid, a sedative, and his studies led him to believe that a drug-platelet complex was antigenic and resulted in the production of antibody, which then reacted with platelets, in the presence of the drug, to produce agglutination and lysis.

The current concept suggests that the drug acts as a hapten. A hapten alone is too small to produce an antibody response, but it combines with some macromolecular substance in plasma, probably a protein, to form an "antigenic complex" which in turn causes the production of antibody. Finally, the "drug-antibody complex" is adsorbed to platelets in a non-specific manner having to do with fixing of complement.

Drugs which produce 7S-type antibodies usually affect platelets. Drugs responsible for the production of 19S antibody are more likely to affect red cells and cause hemolytic anemia.

Proof of the relationship of a drug to a cytopenia is not easy. A rapid study may be performed by adding .2 ml. of saturated solution of the drug and .2 ml. of the patient's serum to 2 ml. of normal blood and observing this for clot retraction. In the case of a drug causing platelet agglutination and lysis the clot retraction is inhibited. Later in the course, the presence of antibody to the drug can be examined by adding .2 ml. of the drug solution to 2 ml. of the patient's blood and again noting inhibition of clot retraction if the drug was responsible for platelet damage.

Treatment

So far as treatment is concerned, the drug should, of course, be stopped at once. This may be all that can be done effectively. However, in an emergency situation, one would generally use steroids in large dosages, as was done in this case, for whatever corticosteroids do to stimulate platelet formation and possibly to affect capillary function and in some way lessen the bleeding tendency. The use of platelet transfusion is somewhat equivocal, since in all likelihood the patient still has circulating drug, and the transfused platelets might also be expected to be destroyed. If the drug has been removed or if the patient has not been on the drug recently, then platelet transfusion might have some benefit in the emergency situation.

Conclusion

This patient had a hemorrhagic disorder leading to her death from cerebral hemorrhage. The bleeding was due to thrombocytopenia which was probably induced by drugs which she had taken for a long period of time.

Clinical Diagnosis: Drug-induced thrombocytopenia. Hemorrhagic diathesis with massive intracerebral hemorrhage.

Pathology

Dr. Herbert Polesky*

Autopsy

The prosector noted *petechiae* involving the upper and lower extremities

*Director, War Memorial Blood Bank, Minneapolis.

and the trunk. *Ecchymoses* were observed at the venipuncture sites and over the left lateral malleolus. On opening the abdominal cavity, *petechial hemorrhages* were noted on the peritoneal surfaces and the serosa of the intestine. The appendix was absent. The heart weighed 300 gm. and was essentially normal except for petechiae over the epicardium. The lungs were normal. The vena cava and femoral veins were carefully dissected and no thrombotic processes found. The spleen weighed 100 gm. and showed foci of *extramedullary hematopoiesis.* The gallbladder was distended and contained calculi. The kidneys showed petechial hemorrhages and there was a small hemorrhage into the right renal pelvis. The bladder showed punctate petechial hemorrhages on the mucosal surface. As expected from the clinical history, the brain contained the major pathology. On opening the dura, *recent and old bilateral subdural hemorrhages* were noted. A large hematoma was present, 2 cm. caudal to the anterior pole of the left frontal lobe extending 7 cm. caudally, also involving the right parietal lobe, the corpus callosum and the ventricular system. There was displacement of the right side of the brain to the left and downward. The conclusions from the anatomic findings suggest multiple bleeding tendencies with *massive cerebral hemorrhage secondary to thrombocytopenia.*

The pathology observed is related specifically to the fact that *platelets somehow preserve endothelial integrity;* in some very interesting electronmicrographs, Van Horn and Johnson showed that red cells, in guinea pigs made thrombocytopenic by irradiation, penetrate the endothelial cells and enter the vessel walls. These penetrations are not necessarily at the cellular junction. In this study the thrombocytopenic guinea pigs were also injected with carbon particles, and similar evidence for changes of endothelial integrity was demonstrated. If platelets were infused into the irradiated animals, these changes were not seen. Thus it seems highly likely that in the patient being presented, the widespread purpura observed is related to a similar mechanism.

If we briefly review the cases of thrombocytopenia, they can be classified first into those with *decreased production* of platelets, subdivided in turn into those with megakaryocytes and those that lack megakaryocytes. The next major category comprises those patients in whom there is *extravascular sequestration,* either splenic or non-splenic. The third category shows *increased destruction,* which can be related to injury, to intravascular utilization as occurs in the consumption coagulopathy syndrome, or to immunologic damage. I think our patient fits into this last category.

The patient demonstrates at least three of the five criteria necessary to make the diagnosis of idiosyncratic thrombocytopenic purpura; there is thrombocytopenia without significant anemia or leukopenia; this patient had megakaryocytes present in normal quantities in her bone marrow and her spleen was not enlarged. The other two criteria to make the diagnosis definitive are evidence for a shortened platelet survival and demonstration of platelet antibody in the patient's serum.

Comments

There is no question that antibodies to platelets can occur and cause thrombocytopenia. Sensitization may be by isoimmunization in patients who have received transfusions or by a fetal-maternal transfer. There are rare reports of delayed thrombocytopenias occurring eight days after transfusion. The specificity of the platelet antibodies is beyond the scope of this discussion. I would only

comment that platelet antigens are related to the HL-A antigens and are shared in some cases, but not always, with leukocytes. There is no clear-cut evidence on the relationship of platelet antigens to red cell antigens.

Immunologic Purpura

Immunologic thrombocytopenic purpura may occur in viral infections, in systemic lupus erythematosus, and in lympho-proliferative diseases. There is also a category of so-called idiopathic cases and, lastly, drug-associated thrombocytopenia. It is into the latter category I think this patient fits.

I would like to be able to tell you that we have definitively shown the presence of platelet antibody in this patient, but unfortunately our studies are somewhat confusing. Several methods can be used to show the presence of platelet antibody; if the antibody-antigen reaction is drug-dependent, this can usually be demonstrated. By the inclusion of the drug in the mixture of patient's serum and *normal* (donor) platelets, one can clearly implicate a specific drug. Available tests included platelet agglutination, antihuman globulin consumption, complement fixation, inhibition of clot retraction, platelet factor 3 release, and complement fixation. Since in most cases the antibody-antigen reaction damages the surface of the platelet, causing it to release its materials, many of these tests are based on measuring the platelet release phenomena. Thus in the clot retraction tests, as referred to by Dr. Green, one incubates the serum from the patient in whom one suspects antibody with platelet-rich plasma from a normal individual. Calcium is added and the test carried out in the presence and absence of drug. If the patient has an antibody to the drug, then clot retraction will be inhibited. Though simple to perform, this test is relatively insensitive. Similarly, platelet factor 3 release is accelerated in the presence of drug-dependent antibody. Both these tests were negative with this patient's serum and with both of the suspect drugs.

The most sensitive technic in our hands has been complement fixation. The test system includes drugs, normal platelets, the patient's serum exogenous complement, and a sensitized sheep cell indicator system. Initial results with this patient's serum suggested that complement fixation was occurring in the appropriate mixtures; however, we ran into some problems, making our results difficult to interpret. First, Vistaril added directly to serum caused a precipitin to form. Second, Vistaril added to red blood cells caused hemolysis; and, lastly, the drug plus platelets without the patient's serum also fixed complement.

Drug-induced Auto-antibody Mechanism

Before concluding my discussion, I think it would be worthwhile taking a few minutes now to look at drug-induced auto-antibody mechanisms. There are three model systems available to explain red cell auto-antibodies, about which more detailed information is available than is known about platelet antibodies (Table). *Penicillin is the most common* and most practicable drug which causes antibody-mediated hemolysis. Since red cell and presumably platelet surfaces can act as carriers for various chemicals, a passive red cell

TABLE

Mechanisms of Drug-Induced "Auto-Antibody"

Complex	Model Drug
1) RBC — Drug + Antidrug Antibody (IgG)	Penicillin
2) Drug—Antidrug Antibody → Activated C′ + RBC	Quinidine
3) a. RBC—"Drug" + Antibody to Normal RBC Antigen	Aldomet
b. RBC + Drug Altered Normal Gamma Globulin	

surface-drug complex is formed. Anti-drug antibody, usually of a 7S variety (IgG), reacts with the drug on the cell surface, leading to sequestration and destruction of the cell. The red cell in this case is an innocent bystander.

In the *second model, a drug which may be attached to protein* or act as a haptene induces anti-drug antibody. When the drug is administered to a patient with antibody, an antibody-drug complex forms, which mediates complement activation. Red cells or platelets, whichever may be the case, may be affected since their surfaces act as target organs for components of the activated complement system. Quinidine is one of the drugs acting by this mechanism. Here again the red cell or platelet is an innocent bystander. It is thought that a similar sort of situation can occur leading to platelet destruction in the presence of viruses and/or bacteria.

The *third model* is not as well worked out as the first two attempts to explain the positive Coombs' tests observed in patients on *a-methyldopa (Aldomet).* Two possible mechanisms have been advanced to explain the experimental observations. It is possible that the drug or a metabolite of the drug attaches to the red cell surface as a haptene, this complex in some way altering the normal Rh antigen and making the erythrocyte auto-antigenic. This then would explain why a patient on Aldomet who develops a positive Coombs' test and/or hemolytic anemia frequently has antibodies with anti-Rh specificity, often similar to an antigen normally found on the patient's own cells or to a "basic Rh substance." Another possibility is that the drug or its metabolite in some way alters normal gamma globulin, changing the affinity of gamma globulin for red cell surfaces and increasing the binding of the gamma globulin to the erythrocytes, eventually leading to their destruction.

Conclusions

In this patient, we suspect that the thrombocytopenia was probably induced by one or both of the drugs the patient was receiving and that the platelets were innocent bystanders. It is not possible to be sure which of the drugs was responsible. Vistaril, a hydroxyzine hydrochloride, has not been reported to cause toxic effects on the liver or bone marrow even when administered for long periods of time; and Stelazine, a phenothiazine derivative, is thought to have a wide margin of safety. However, occasional cases of agranulocytosis, thrombocytopenia, pancytopenia, anemia, etc. have been reported following the use of the phenothiazines.

In conclusion, I think the diagnosis in this case is most likely immunologic thrombocytopenic purpura with massive intracerebral hemorrhage as the cause of death.

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7-12. May be secured from the author or the reprints.

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neutropenia and thrombocytopenia; however
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Review

Microangiopathic Hemolytic Anemia

Review and Report of Two Cases

SIMON G. SAX, M.D.* AND MILTON H. SAX, M.D.*

We should like to report two cases of microangiopathic hemolytic anemia—one secondary to metastatic carcinoma and the other to malignant hypertension.

Definition and Review

Microangiopathic hemolytic anemia is a disorder characterized by hemolysis and by contracted, distorted, and fragmented red cells. This type of anemia can be diagnosed by examining a fresh peripheral blood smear. The presence of schizocytes, helmet cells, burr cells, triangular cells, and other fragmented red cells establishes the diagnosis. If an examiner is unfamiliar with this blood picture, he may report "anisocytosis or poikilocytosis" without specifically commenting on these bizarre cells.

As early as 1892, Paul Ehrlich described fragmented cells, or "schizocytes," in anemias.[1] He believed a chemical or toxin fragmented the red cells. Later, Schwartz and Motto noted burr cells —a red cell about the size of a mature erythrocyte but with spiny projections at its periphery.[2] The burr cell, incidently, is not a crenated cell.

Associated Conditions

Brain, Dacie, and Hourihane, who coined the term "microangiopathic hemolytic anemia," reported it in association with thrombotic thrombocytopenic purpura, acute glomerulonephritis of infancy and childhood, renal cortical necrosis, polyarteritis nodosa, malignant hypertension, and carcinomatosis.[3] Others have observed microangiopathic hemolytic anemia in connection with septicemia, renal transplant rejection, a large leiomyoblastoma, cardiac valve replacement, preeclampsia, and abruptio placenta.[4-10]

Pathogenesis

The diseases or conditions just mentioned share one thing in common—narrowing of capillaries and other small blood vessels by thrombi. In the case of dessiminated carcinoma, these thrombi are composed of tumor cells. As red cells pass through the microcirculation, they are forced through the mesh of fibrin strands of intravascular thrombi or entrapped carcinoma cells. This action fractures the erythrocytic envelope, because turbulence and shearing forces mechanically injure the red cell membrane. Schizocytes, burr cells, helmet cells, and triangular cells result and can be easily seen in the peripheral blood. The process has been reproduced *in vivo* and observed *in vitro*.[11,12]

Case Reports

Case 1

A 58-year-old white woman was admitted to St. Mary's Hospital in Duluth on January 28, 1969. She complained of sharp, left-sided chest pain, exertional dyspnea, fatigue, and swollen ankles.

In September, 1967, a right radical mastectomy for an intraductal carcinoma had been performed elsewhere. The tumor had spread to the right axillary nodes, and she received postoperative radiation therapy.

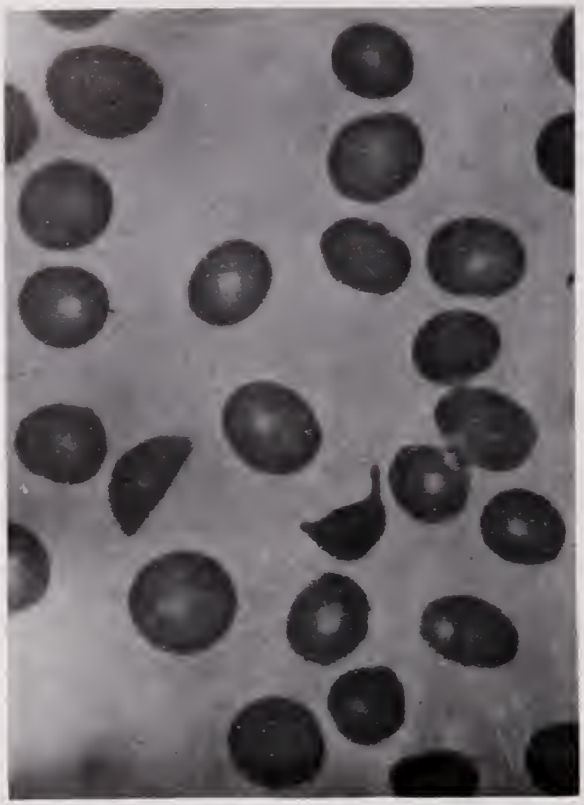
On physical, she complained of chest discomfort. Other than her well-healed mastectomy scar, there were no positive findings. She had no palpable nodes, organs, or recurrent tumor in her incision.

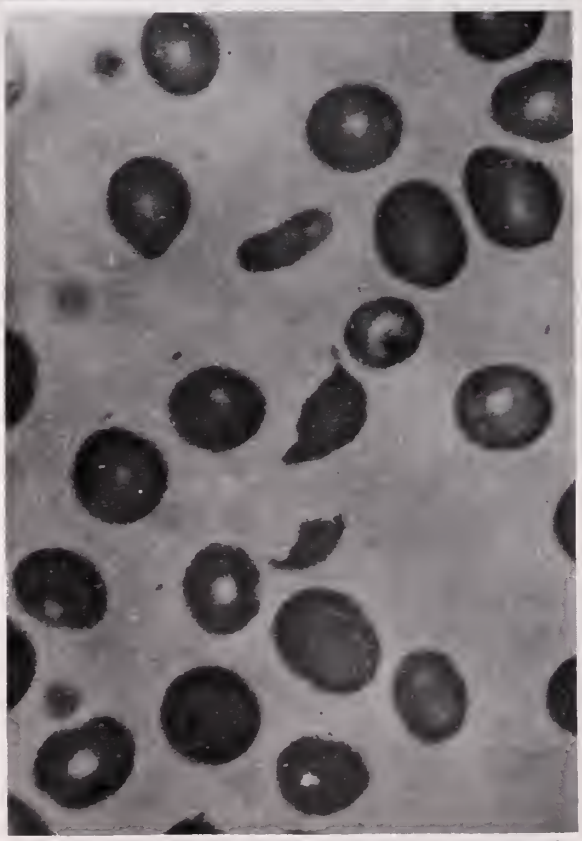
An admission electrocardiogram was normal with a normal recheck electrocardiogram in 48 hours. Chest x-ray was negative except for an absent right breast.

Laboratory Data

The white blood count and differential smear were normal and remained so. Hemoglobin levels fluctuated between 8 and 10 gms.%, and the red blood count averaged 2.5 million/mm.^{3} Hematocrit ranged from 25 to 30 volumes %. Sedimentation rates were elevated, persisting between 45 and 60 mm/hour. Reticulocytes numbered 4.9% on admission, rising as high as 11.2% and averaging 8%. The peripheral blood smear revealed normal platelets. Nucleated red blood cells numbered as high as 14/100 WBC on different examinations. Helmet cells and schizocytes (red blood cell fragments) were common (Figures 1 and 2). Bone marrow examination (Figure 3) demonstrated marked normoblastic erythroid hyperplasia. In addition, both smears and sections of the marrow sample revealed metastatic carcinoma cells.

*Duluth, Minnesota.





Figures 1 (top) and 2 (bottom)—Portions of identical peripheral blood smear: Helmet cell and schizocytes are demonstrated. Wright's stain X 1800.

Normal laboratory results included: bleeding time; clotting time; serum iron and iron binding capacity; direct and indirect Coombs' test; vitamin B12 absorption test; fecal guaiac tests; serum levels of glucose, transaminase, sodium, potassium, calcium, phosphorus, uric acid, cholesterol, total protein, albumin and bilirubin; urinalysis; gastric acidity; and blood cultures. Blood urea nitrogen remained below 18 mgs.% until the last two weeks of life when it gradually rose to a terminal level of 62 mgs.%.

Course

The condition of the patient progressively deteriorated. She became deeply jaundiced. Her liver became enlarged and was palpable 4 cms. below the right costal margin. Palpation of the edges and contour of the liver indicated a generalized enlargement.

She expired on April 2, 1969, 74 days after admission. Permission for an autopsy was not given.

Case 2

A 60-year-old white man was admitted to St. Luke's Hospital in Duluth, in a state of semi-stupor on December 1, 1969. He was weak, partially disoriented, incoherent, incontinent of urine, and had severe generalized headaches. His wife stated that he had had the "flu" for about three days and had fallen several times at home.

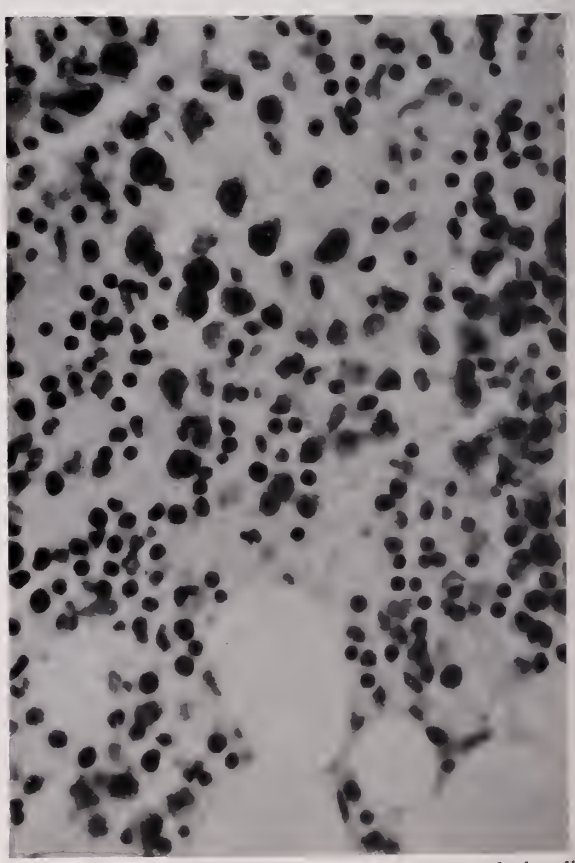


Fig. 3—Bone marrow: Tissue section. Large, dark cells represent metastatic carcinoma cells. Hematoxylin and eosin stain X 1200.

In April of 1968, at St. Mary's Hospital in Duluth, he had a similar but less severe acute episode with severe headaches, semi-stupor, and marked hypertension. Between hospitalizations, the patient received antihypertensive medications and potassium supplement. His wife was not able to say how long he had been hypertensive.

Physical Examination

Examination revealed a well developed, well nourished, semi-stuporous white man. The pupils were pinpoint, and did not accommodate or react to light. (Later in his hospitalization the funduscopic examination revealed A-V compression and a few flame-shaped fundal scars.) There was some neck rigidity. The heart tones were rapid, booming, and free from murmurs. The admission blood pressure was 290/200. Examination of the lung fields, abdomen, prostate, and extremities revealed no abnormal findings, and neurological examination was normal.

Laboratory Data

Laboratory studies included a white blood count of 8000/mm^3 with a normal differential count. Hemoglobin levels ranged from 10 gms.% early in his illness to 8 gms.% at the height of his uremia. Reticulocyte counts averaged 3.0%. His sedimentation rates varied from 100 to 150 mm/hr. Urinalysis revealed 4 plus proteinuria. This gradually subsided to 1 plus during hospitalization, but the urine specific gravity remained constant at 1.011.

Pheochromocytoma and aldosteronism seemed improbable with normal results for determinations of urinary vanillic mandelic acid, 24-hour sodium and potassium excretion and serum sodium level. Serum potassium at admission was 3.3 meq./L, and slowly rose to 5.5 meq./L. Serum iron, iron binding capacity, total protein, acid phosphatase, lactic dehydrogenase, cholesterol, calcium, phosphorus, bilirubin, alkaline phosphatase and transaminase were normal. The urinary renin was reported as normal.

Blood urea nitrogen value on admission was 78 mgs.%, rising to a maximum of 204 mgs.% over the next three weeks, declining again to 27 mgs.% upon discharge about six weeks after admission. The blood creatinine was elevated along with the blood urea nitrogen to 5.8 mgs.% at its height, later declining to normal levels.

Peripheral Smear

The peripheral blood smear (Figure 4) demonstrated helmet cells, burr cells and other evidence of erythrocyte fragmentation which improved gradually but had not totally disappeared upon discharge (Figure 5). Bone marrow aspiration (Figure 6) demonstrated erythroid normoblastic hyperplasia.

Miscellaneous Studies

Studies in the latter part of his hospitalization yielding normal results included barium study of the stomach and duodenum, intravenous pyelography and skull x-rays. Because of a history of alcoholism, a liver scan, following injection of 200 uc. of Au^{198}, was done and found to be normal. Admission electrocardiogram was normal except for evidence of left ventricular hypertrophy. Bedside chest x-ray was normal.

Course

For the acute hypertensive crisis 2.5 mgs. reserpine subcutaneously at intervals of four hours, was administered for two injections so that the blood pressure became 200/120. Treatment also included careful management of fluid intake, observation of electrolytes, antibiotics, an indwelling catheter with a urometer, and digitalization. Dialysis, while considered, was not performed since we felt it of doubtful merit in a patient of his age and probable pathology. A secondary gout developed due to uremia and antihypertensive medication. Response to ACTHAR-GEL® and Col-Benemid® was good.

The patient had a stormy and agonizing clinical course during hospitalization. The hypertensive encephalopathy and malignant hypertension, present on admission, gradually improved. Periods of moderate oliguria to marked diuresis with isosthenuria occured.

When discharged on January 26, 1970, the patient was alert and comfortable. Aldactazide® with dietary potassium supplements was prescribed.

Comment and Discussion

In Case 1, the fragmentation of the erythrocytes is demonstrated in the photomicrographs (Figures 1 and 2). This probably resulted from partially occluding nests of cancer cells (Figure 3), observed in the bone marrow. The peripheral red blood cell morphology, characteristic of microangiopathic hemolytic anemia, was the initial objective finding of metastatic carcinoma, later con-

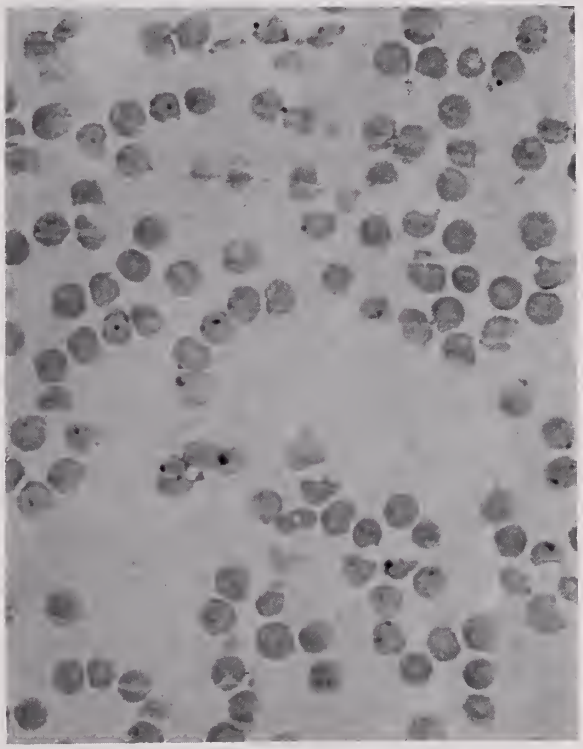


Fig. 4—Peripheral blood smear. Wright's stain X 750. Patient's smear taken before treatment. Note the helmet cells and fragmentation of red blood cells.

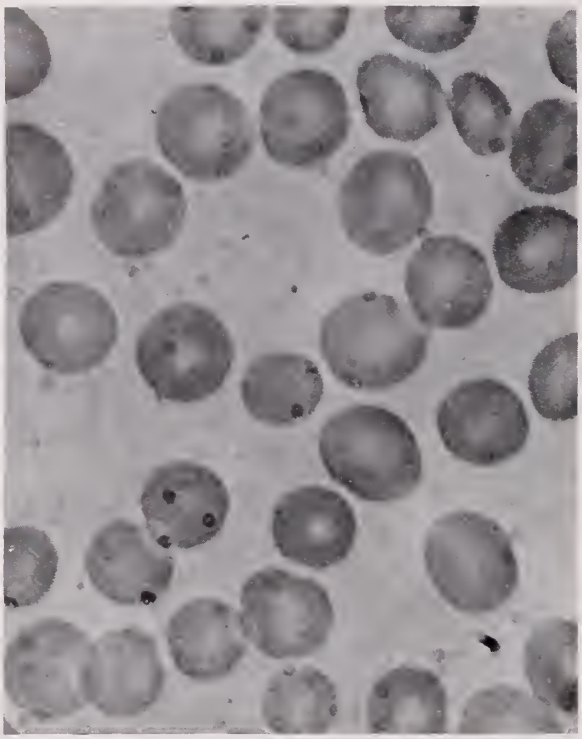


Fig. 5—Peripheral smear taken after treatment. Wright's stain X 1000. Still shows some but less fragmentation and distortion of red blood cells.

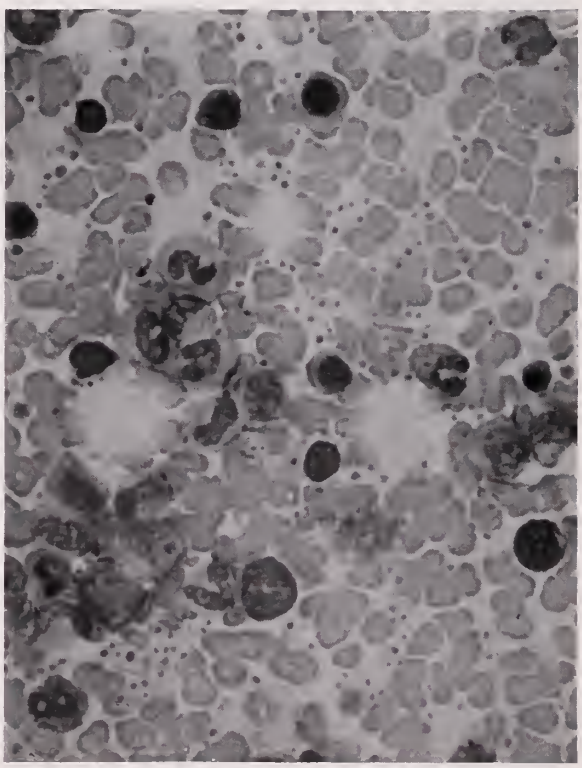


Fig. 6—Bone marrow taken on patient before treatment X 750. Note the erythroid hyperplasia of normocytic type. Background cells show fragmentation and helmeting.

firmed by bone marrow study.

Reticulocytosis differentiates microangiopathic hemolytic anemia from a myelophthisic type of anemia, which is seen when bone marrow is replaced more completely by cancer cells.

Her platelet count was elevated to 588,000 when she was hospitalized in September of 1967 for surgery. An increased platelet count has been previously noted in carcinoma, as well as increased clotting tendency.

Case 2 demonstrates that microangiopathic hemolytic anemia can complicate malignant hypertension with hypertensive encephalopathy. During the interval between the two hospital admissions, antihypertensive medications with potassium supplements were prescribed but the patient may have taken the medications erratically. This would explain the hypokalemia on admission.

Isosthenuria was observed in his hospitalization and later in the office. When last in the office on June 14, 1971, the patient's blood pressure was 164/90, and he was free of complaints. He has been maintained on one tablet twice daily of Aldactazide® with dietary potassium supplementation.

During his hospital course, his red cell fragmentation lessened as his blood pressure and blood urea nitrogen fell (Figure 4). Photomicrographs IV and V, before and after therapy, document this improvement. Aherne[14] has pointed out that presence of burr cells in the circulating blood or other degree of erythrocyte distortion does not completely correlate with the degree of azotemia, but should warn that renal failure is impending. Our observations confirm this. Residual evidence of erythrocyte fragmentation may represent persistence of a small degree of microthrombosis.

The mechanism of erythrocyte fragmentation in malignant hypertension is not firmly established, but higher arterial pressure and vascular disease could cause a greater permeability of the smaller vessels to fibrinogen (Factor I), with fibrin deposition on the vascular wall, narrowed lumen, impaired fibrinolysis,[15] and finally microthrombosis. Kidney biopsies in such patients do not always demonstrate an anatomical change.[16] The turbulence and increased hydrostatic pressure in essential hypertension is not sufficient to cause erythrocytic fragmentation.

Summary

We have reported two cases of microangiopathic hemolytic anemia. The first, a 58-year-old woman, had a metastatic breast carcinoma as the cause of her anemia. The second patient, a 60-year-old man, had malignant hypertension as the genesis of his hemolytic state. Both patients had characteristic fractured red cells—in the form of helmet cells, burr cells, schizocytes, and triangular cells in their peripheral smears. The woman died 74 days after admission in hepatorenal failure. The man survived, despite severe hypertension and azotemia. As his blood pressure fell and his renal function improved, his peripheral smear showed less and less red cell fragmentation.

Acknowledgement

We thank Dr. A. C. Aufderheide of the Department of Pathology at St. Mary's Hospital, Duluth, and Dr. D. L. Michaelis of the Department of Pathology at St. Luke's Hospital, Duluth, for their kindness in supplying photomicrographs and reviewing our manuscript.

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Medicine in the Nineteenth Century

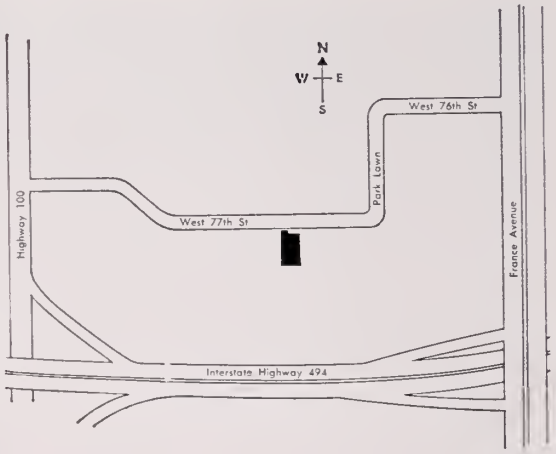
Surgery was furthered by several developments. One came about when Joseph Lister, who believed with Pasteur that bacteria are all over everything, thought that they should be kept from crawling into the wound opened by the surgeon. What Pasteur had done to milk, Lister proposed doing to hands before an operation. When Lister appeared before a gathering of surgeons and suggested, "Maybe you should be sterilized," they thought he was going a little too far. Even when they understood that he merely wanted them to boil their hands, they were uncooperative. Finally Lister said that if they just washed their hands, this would help. This revolutionary practice, taken up with some reluctance in England and France, eventually spread to the United States, where it was hailed by the manufacturers of soap. Lister also developed a carbolic acid spray, used as an antiseptic on the wound itself. After surgery, just before closing the wound, Lister would get out his hand pump and, turning to his colleagues, solemly say, "Let us spray."*

*Richard Armour: It All Started with Hippocrates, 1966.

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Contraindications
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Warnings
When weight loss is unsatisfactory the recommended dosage should not be increased in an attempt to obtain increased anorexigenic effect; discontinue the drug. Tolerance to the anorectic effect may develop. Drowsiness or stimulation may occur and may impair ability to engage in potentially hazardous activities such as operating machinery, driving a motor vehicle, or performing tasks requiring precision work or critical judgment. Therefore, such patients should be cautioned accordingly. Caution must be exercised if Pre-Sate (chlorphentermine hydrochloride) is used concomitantly with other central nervous system stimulants. There have been reports of pulmonary hypertension in patients who received related drugs.

Drug Dependence Drugs of this type have a potential for abuse. Patients have been known to increase the intake of drugs of this type to many times the dosages recommended. In long-term controlled studies with the high dosages of Pre-Sate, abrupt cessation did not result in symptoms of withdrawal.

Usage In Pregnancy The safety of Pre-Sate (chlorphentermine hydrochloride) in human pregnancy has not yet been clearly established. The use of anorectic agents by women who are or who may become pregnant, and especially those in the first trimester of pregnancy, requires that the potential benefit be weighed against the possible hazard to mother and child. Use of the drug during lactation is not recommended. Mammalian reproductive and teratogenic studies with high multiples of the human dose have been negative.

Usage In Children Not recommended for use in children under 12 years of age.

Precautions
In patients with diabetes mellitus there may be alteration of insulin requirements due to dietary restrictions and weight loss. Pre-Sate (chlorphentermine hydrochloride) should be used with caution when obesity complicates the management of patients with mild to moderate cardiovascular disease or diabetes mellitus, and only when dietary restriction alone has been unsuccessful in achieving desired weight reduction. In prescribing this drug for obese patients in whom it is undesirable to introduce CNS stimulation or pressor effect, the physician should be alert to the individual who may be overly sensitive to this drug. Psychologic disturbances have been reported in patients who concomitantly receive an anorectic agent and a restrictive dietary regimen.

Adverse Reactions
Central Nervous System: When CNS side effects occur, they are most often manifested as drowsiness or sedation or overstimulation and restlessness. Insomnia, dizziness, headache, euphoria, dysphoria, and tremor may also occur. Psychotic episodes, although rare, have been noted even at recommended doses. **Cardiovascular:** tachycardia, palpitation, elevation of blood pressure. **Gastrointestinal:** nausea and vomiting, diarrhea, unpleasant taste, constipation. **Endocrine:** changes in libido, impotence. **Autonomic:** dryness of mouth, sweating, mydriasis. **Allergic:** urticaria. **Genitourinary:** diuresis and, rarely, difficulty in initiating micturition. **Others:** Paresthesias, sural spasms.

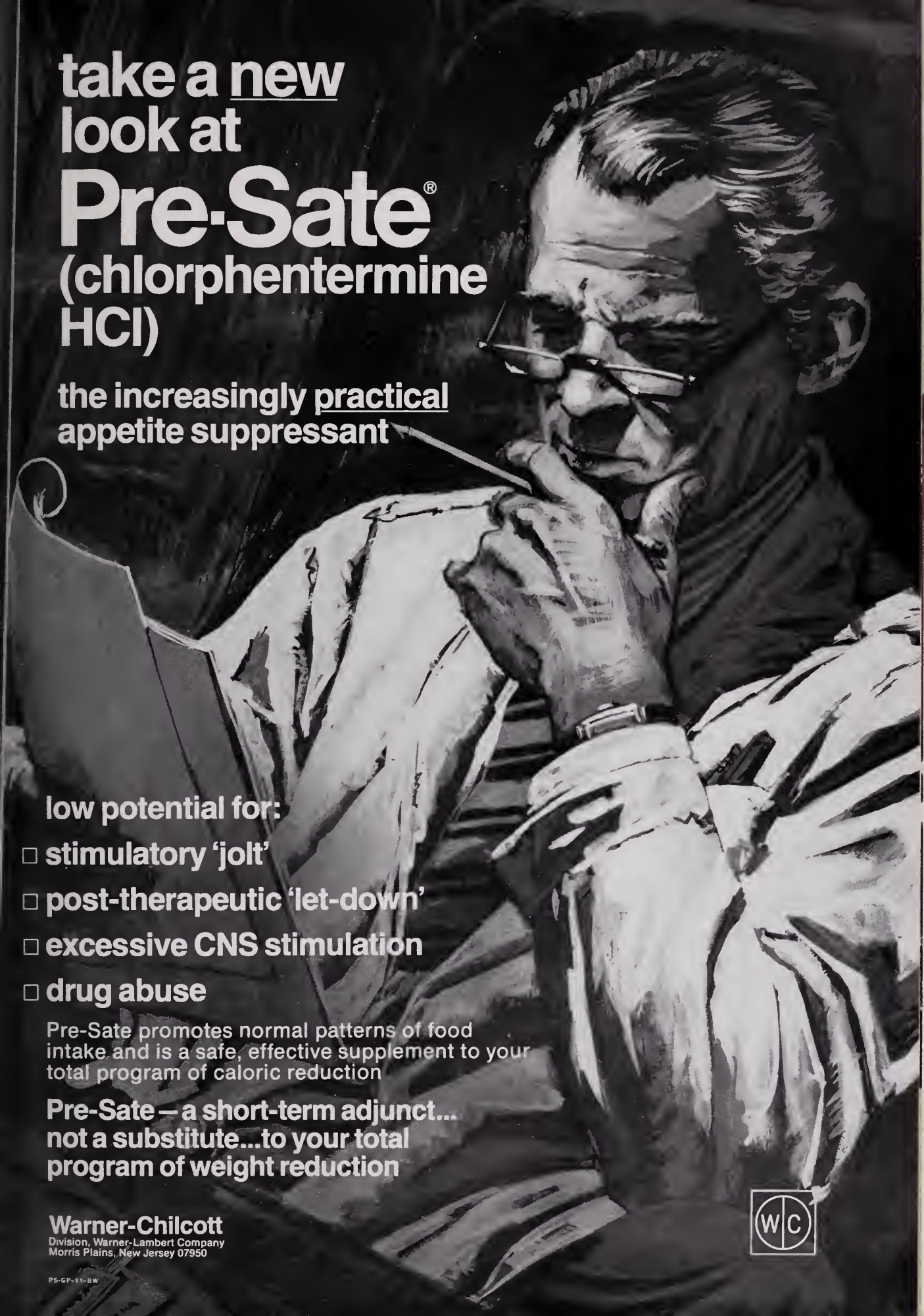
Dosage and Administration
The recommended adult daily dose of Pre-Sate (chlorphentermine hydrochloride) is one tablet (equivalent to 65 mg chlorphentermine base) taken after the first meal of the day. Use in children under 12 not recommended.

Overdosage
Manifestations: Restlessness, confusion, assaultiveness, hallucinations, panic states, and hyperpyrexia may be manifestations of acute intoxication with anorectic agents. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension, or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management: Management of acute intoxication with sympathomimetic amines is largely symptomatic and supportive and often includes sedation with a barbiturate. If hypertension is marked, the use of a nitrate or rapidly acting alpha-receptor blocking agent should be considered. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

How Supplied
Each Pre-Sate (chlorphentermine hydrochloride) tablet contains the equivalent of 65 mg chlorphentermine base; bottles of 100 and 1000 tablets.

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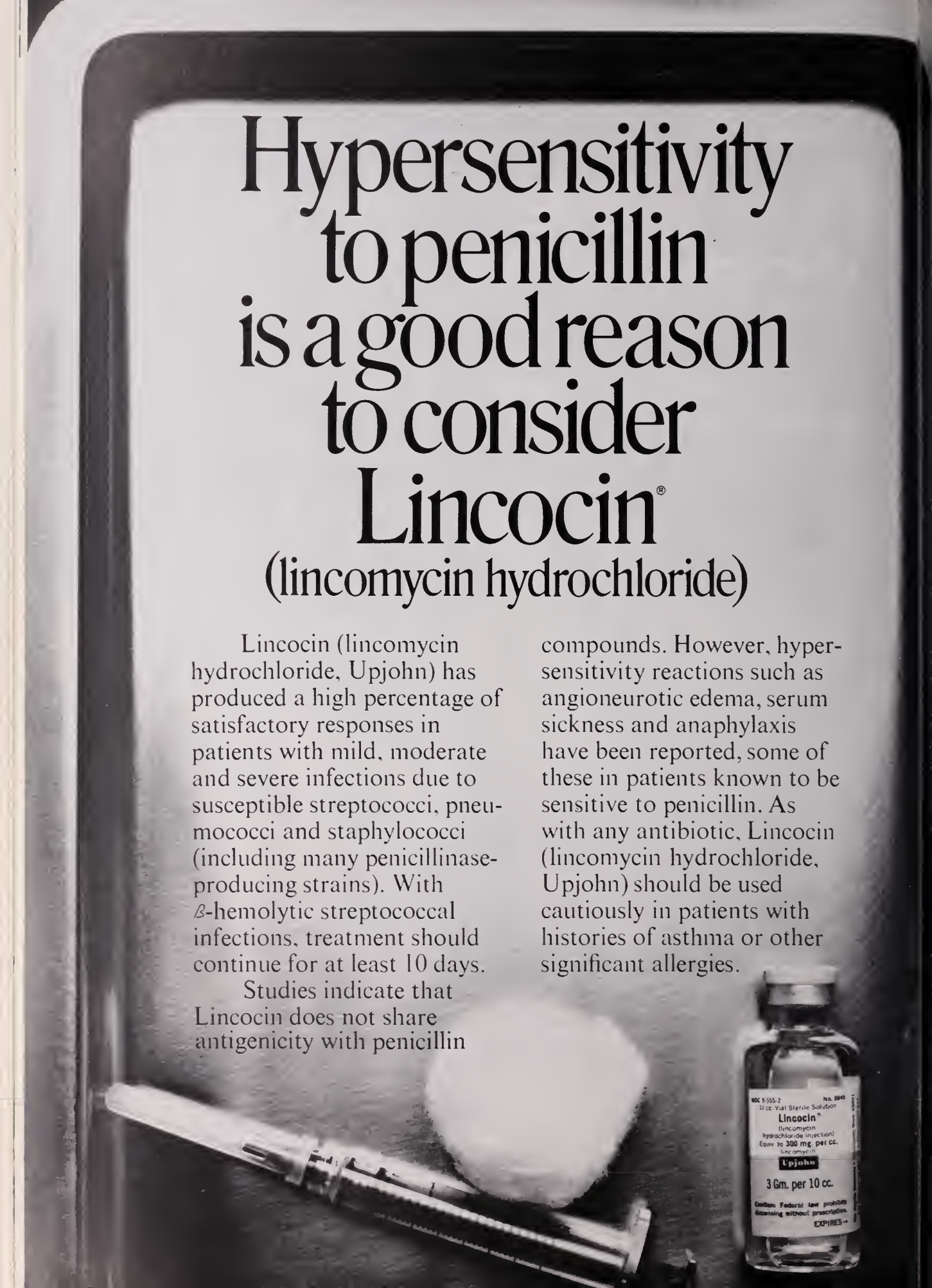

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(lincomycin hydrochloride)

Lincocin (lincomycin hydrochloride, Upjohn) has produced a high percentage of satisfactory responses in patients with mild, moderate and severe infections due to susceptible streptococci, pneumococci and staphylococci (including many penicillinase-producing strains). With β-hemolytic streptococcal infections, treatment should continue for at least 10 days.

Studies indicate that Lincocin does not share antigenicity with penicillin compounds. However, hypersensitivity reactions such as angioneurotic edema, serum sickness and anaphylaxis have been reported, some of these in patients known to be sensitive to penicillin. As with any antibiotic, Lincocin (lincomycin hydrochloride, Upjohn) should be used cautiously in patients with histories of asthma or other significant allergies.



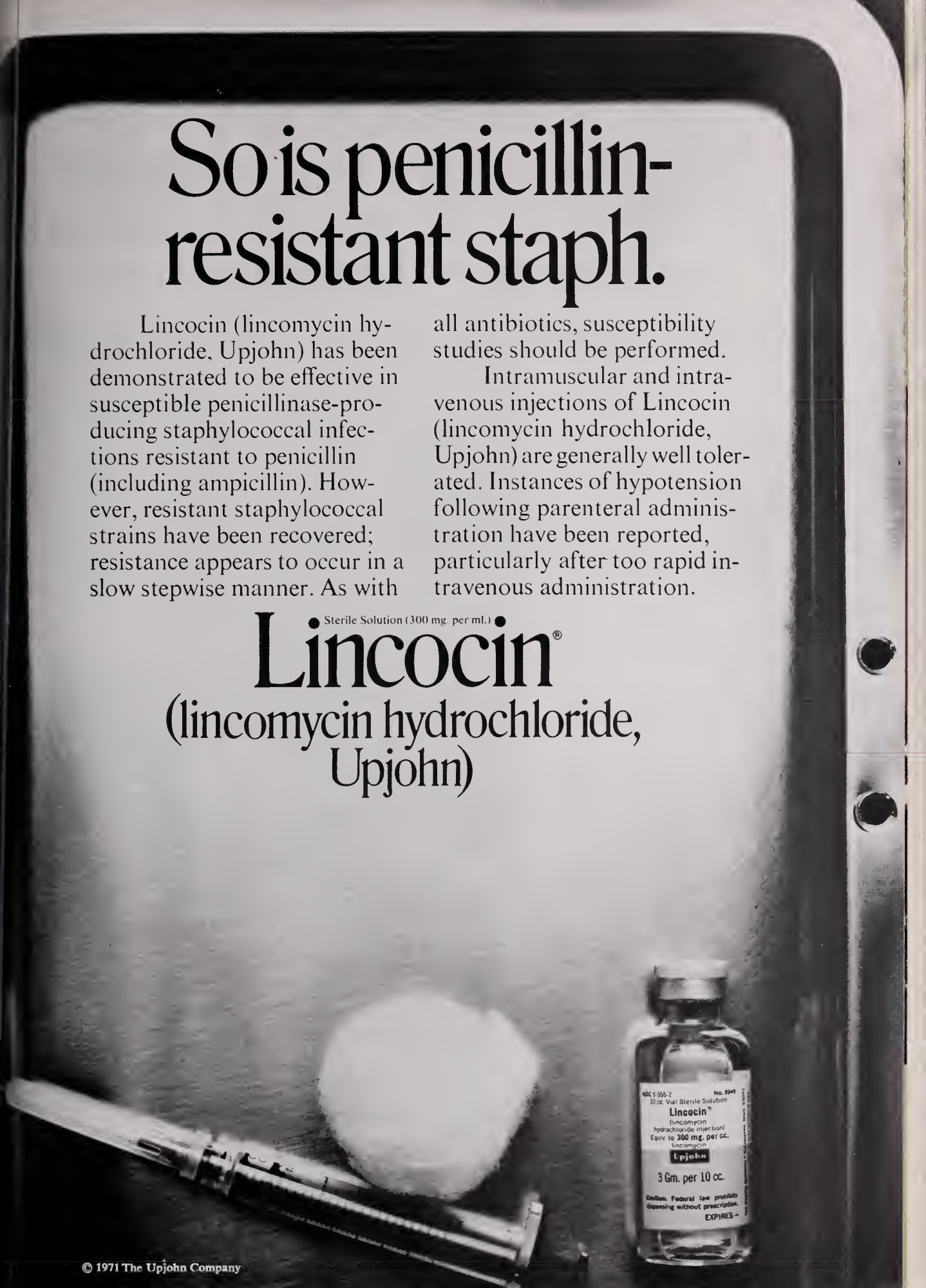
So is penicillin-resistant staph.

Lincocin (lincomycin hydrochloride, Upjohn) has been demonstrated to be effective in susceptible penicillinase-producing staphylococcal infections resistant to penicillin (including ampicillin). However, resistant staphylococcal strains have been recovered; resistance appears to occur in a slow stepwise manner. As with all antibiotics, susceptibility studies should be performed.

Intramuscular and intravenous injections of Lincocin (lincomycin hydrochloride, Upjohn) are generally well tolerated. Instances of hypotension following parenteral administration have been reported, particularly after too rapid intravenous administration.

Sterile Solution (300 mg. per ml.)

Lincocin®
(lincomycin hydrochloride, Upjohn)



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Sterile Solution (300 mg. per ml.)

Lincocin®

(lincomycin hydrochloride, Upjohn) for respiratory tract, skin, soft-tissue, and bone infections due to susceptible streptococci, pneumococci, and staphylococci

Each preparation contains:	Lincomycin hydrochloride monohydrate equivalent to lincomycin base
250 mg. Pediatric Capsule	250 mg.
500 mg. Capsule	500 mg.
*Sterile Solution per 1 ml.	300 mg.
Syrup per 5 ml.	250 mg.

*Contains also: Benzyl Alcohol 9 mg.; and, Water for Injection—q.s.

An antibiotic chemically distinct from others available, indicated in infections due to susceptible strains of staphylococci, pneumococci, and streptococci. *In vitro* susceptibility studies should be performed.

CONTRAINDICATIONS: History of prior hypersensitivity to Lincocin (lincomycin hydrochloride). Not indicated in the treatment of viral or minor bacterial infections.

WARNINGS: Cases of severe and persistent diarrhea have been reported and at times drug discontinuance has been necessary. This diarrhea has been occasionally associated with blood and mucus and at times has resulted in acute colitis. This reaction usually has been associated with oral therapy, but occasionally has been reported following parenteral therapy. Although cross sensitivity to other antibiotics has not been demonstrated, make careful inquiry concerning previous allergies or sensitivities to drugs. Safety for use in pregnancy has not been established and Lincocin is not indicated in the newborn. Reduce dose 25 to 30% in patients with severe impairment of renal function.

PRECAUTIONS: Like any drug, Lincocin should be used with caution in patients having a history of asthma or significant allergies. Overgrowth of nonsusceptible organisms, particularly yeasts, may occur and require appropriate measures. Patients with pre-existing monilial infections requiring Lincocin therapy should be given concomitant antimonilial treatment. During prolonged Lincocin therapy, periodic liver function studies and blood counts should be performed. Not recommended (inadequate data) in patients with pre-existing liver disease unless special clinical circumstances indicate. Continue treatment of β-hemolytic streptococci infection for ten days to diminish likelihood of rheumatic fever or glomerulonephritis.

ADVERSE REACTIONS: *Gastrointestinal*—Glossitis, stomatitis, nausea, vomiting. Persistent diarrhea, enterocolitis, and pruritus ani. *Hemopoietic*—Neutropenia, leukopenia, agranulocytosis, and thrombocytopenic purpura have been reported. *Hypersensitivity reactions*—Hypersensitivity reactions such as angioneurotic edema, serum sickness, and anaphylaxis have been reported, sometimes in patients sensitive to penicillin. If allergic reaction occurs, discontinue drug. Have epinephrine, corticosteroids, and antihistamines available for emergency treatment. *Skin and mucous membranes*—Skin rashes, urticaria, vaginitis, and rare instances of exfoliative and vesiculobullous dermatitis have been reported. *Liver*—Although no direct relationship to liver dysfunction is established, jaundice and abnormal liver function tests (particularly serum transaminase) have been observed in a few instances.



Cardiovascular—Instances of hy[po]sion following parenteral administ[ra]tio have been reported, particularly aft[er] rapid I.V. administration. Rare ins[tan]ces of cardiopulmonary arrest have be[en] reported after too rapid I.V. administ[ra]tion. If 4.0 grams or more administered, [it] dilute in 500 ml. of fluid and adm[in]ister no faster than 100 ml. per hour. [Lo]cal *reactions*—Excellent local tolerance [has] been demonstrated to intramuscularly administ[ered] Lincocin. Reports of pain following in[tra]muscular injection have been infrequent. Intravenous administration of Lincocin in 25[0] to 500 ml. of 5% glucose in distilled water or normal saline has produced no local irritation or phlebitis.

HOW SUPPLIED: *250 mg. and 500 mg.* Capsules—bottles of 24 and 100.

Sterile Solution, 300 mg. per ml.—[in] 10 ml. vials and 2 ml. syringe.

Syrup, 250 mg. per 5 ml.—60 ml. and pint bottles.

For additional product information, consult the package insert or see your Upjohn representative.

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Book Reviews

The best part of every author is in general to be found in his book—SAMUEL JOHNSON.

DISEASES OF BONE AND JOINTS; Louis Lichenstein; Publisher: C. V. Mosby Company, St. Louis, Missouri; Price: $17.50; Pages: 227; Illustrations: 287.

This is a well documented and beautifully illustrated book on the diseases of bone and joints. It is written by a clinical professor of pathology and deals with the etiological and physiologic factors which produce the pathologic changes.

Each chapter has its own bibliographic references and the index is well prepared.

Though there is no specific reference to the typical signs and symptoms of each of these diseases, there is no need for them. Anyone who is interested in a bone or joint disease should refer to this excellent monograph to supplement his basic knowledge with these fundamentally important items of pathologic changes.

Carl O. Rice, M.D.
Minneapolis, Minnesota

BENIGN DISEASES OF THE VULVA AND VAGINA. Herman L. Gardner, M.D., and Raymond H. Kaufman, M.D. The C. V. Mosby Company, St. Louis, 1969, 359 pp., 404 illustrations and two color plates. $23.50.

This book, written by two gynecologists, one of whom is also a pathologist, is an authoritative and comprehensive account of neoplastic, traumatic, dermatologic, and infectious diseases of the vagina and vulva. There are also chapters dealing with the anatomy, embryology, and developmental anomalies of these organs.

The chapter on vulvar dystrophies unscrambles the relationships and terminology used by gynecologists and dermatologists to describe such vulvar entities as atypical epithelial hyperplasia, dysplasia, lichen simplex chronicus, neurodermatitis, lichen planus, atrophic dystrophy, lichen sklerosis et atrophicus, kraurosis, and leucoplakia. This chapter will foster a better understanding of these dermatologic terms, lesions, and treatment now so poorly understood by most gynecologists who will surely shed a tear as they note the passing into obsolescence of the terms kraurosis and leucoplakia.

The chapters on vulvovaginitis are especially noteworthy and reflect Dr. Gardner's basic work and expertise in this field.

There are many clear and instructive photomicrographs to illustrate most of the important diseases discussed. The references are numerous and pertinent.

This book should be in the library of every gynecologist who wishes to better understand and treat the many vulgovaginal diseases seen in his office practice.

Konald A. Prem, M.D.
Minneapolis, Minnesota

"COOKING FOR YOUR CELIAC CHILD (DIETARY MANAGEMENT IN MALABSORPTION SYNDROME)" by Charlotte Baum Sheedy and Norman Keifetz. The Dial Press, Inc., New York, 1969. Price: $5.95.

At last a cookbook for the celiac child has been published, the prescribing of which will give the clinician power to do a better job of dietary counseling than the dietitian, unless she recommends the same book. Unquestionably, the most valuable publication in recent years for parents of a child with celiac disease! This book will be equally valuable for and appreciated by the older person who is suffering from the adult variety of this disease. The doctor who prescribes "Cooking For Your Celiac Child" should page through, and preferably read, the introduction to see how skillfully this book has been written to be adaptable to the medical management which he will prescribe. If he reads further and looks at the recipes, he may find some that he would like to try at home.

Warren J. Warwick, M.D.
Minneapolis, Minnesota

ARROWS OF MERCY; Author: Philip Smith; Publisher: Doubleday Canada Limited, Toronto; Doubleday & Company, Inc., Garden City, New York; Pages: 244; Price: $5.95.

Arrows of Mercy is written by a former editor and feature writer who has the ability to put into interesting prose some very fascinating stories with regard to the discovery of curare in the jungles of the Amazon and trace its utilization in its modern use in anesthesiology.

The jungle stories are thrilling and often hazardous and should fire the imagination of anyone who has an adventurous nature.

Many of the stories, however, have been lost to the reader by the absence of titles to the chapters and headings to the more intimate stories. One speculates, for instance, that "The Pill" might have been discovered years ago had some of the witch medicines of the bachelor girls of the forest who never conceived been more thoroughly investigated after having been initially suggested by the Gill-Merrill expedition. Had the author made it possible for the editor to identify these fascinating stories the reader would have gained a great deal more pleasure.

Carl O. Rice, M.D.
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SEPTEMBER, 1971

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Dalmane (flurazepam HCl) 30 mg reduced awake time—both before and after falling asleep - by fifty percent of pretreatment values in patients with insomnia.[1,2]

Two sleep laboratory studies recently confirmed findings of earlier studies of this type, namely, that Dalmane 30 mg was effective in patients who had trouble falling asleep, staying asleep or both. One 30-mg capsule of Dalmane usually induced sleep within 22 minutes, decreased the number of awakenings and the wake time after the onset of sleep, and provided 7 to 8 hours of sleep without need to repeat dosage during the night.

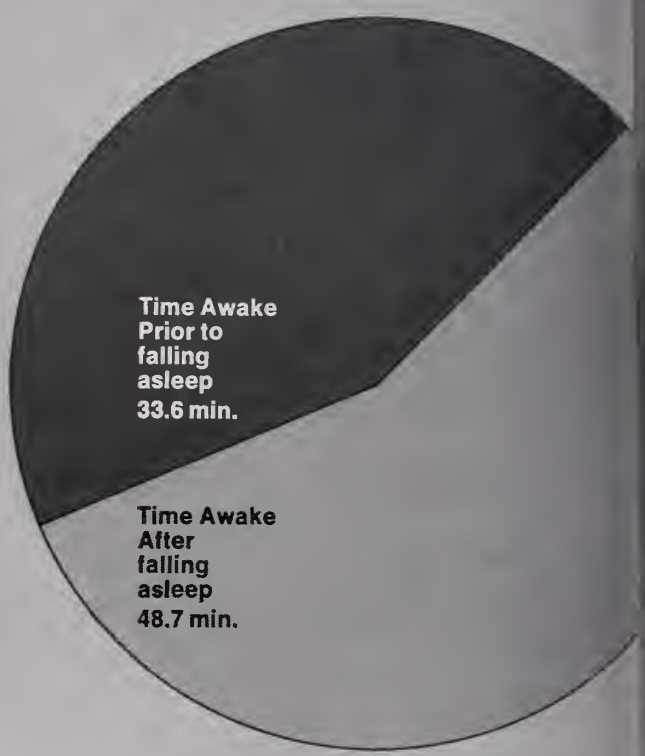
These studies utilized identical protocols and included eight insomniac patients. Sleep laboratory measurements in a limited number of patients are derived from all-night electro-encephalographic, electro-oculographic and electromyographic tracings. Unlike traditional methods of evaluation, they are quantitative, reproducible and projectable to large numbers of subjects.

Results shown represent average values in all subjects for the three consecutive nights of placebo administration prior to Dalmane therapy and the seven consecutive nights on Dalmane 30 mg.

Dalmane is also relatively safe, as reported in clinical studies. Instances of morning "hang-over" have been relatively infrequent; paradoxical reactions (excitement) and hypotension have been rare. Dizziness, drowsiness, lightheadedness and the like were the side effects noted most frequently, particularly in the elderly or debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

References: 1. Frost, J. D., Jr.: "A System for Automatically Analyzing Sleep," Scientific Exhibit presented at Clinical Convention, A.M.A., Boston, Nov. 29-Dec. 2, 1970, and Aerospace M.A., Houston, April 26-29, 1971.
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley, N.J.

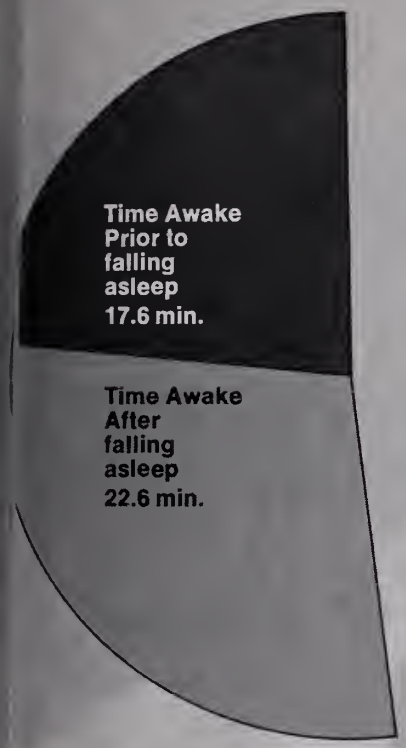
Before Dalmane (flurazepam HCl)



Measurements of sleep in the sleep laboratory are obtained with electroencephalographic, electro-oculographic and electromyographic recordings.

ıd slept through the night

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Dlmane
(ıurazepam HCl)



sleep laboratory measurements in cited studies

ter	Before Dalmane	On Dalmane
quired to fall asleep	33.6 min.	17.6 min.
me after onset of sleep	48.7 min.	22.6 min.
of wakeful periods after of sleep	12.2	8.4
eep time	420.0 min.	447.5 min.
eep percent	88.6	94.5

ıical effectiveness as ›ven in the sleep laboratory

)almane®
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30-mg capsule h.s.—usual adult dosage.
15-mg capsule h.s.—initial dosage for rly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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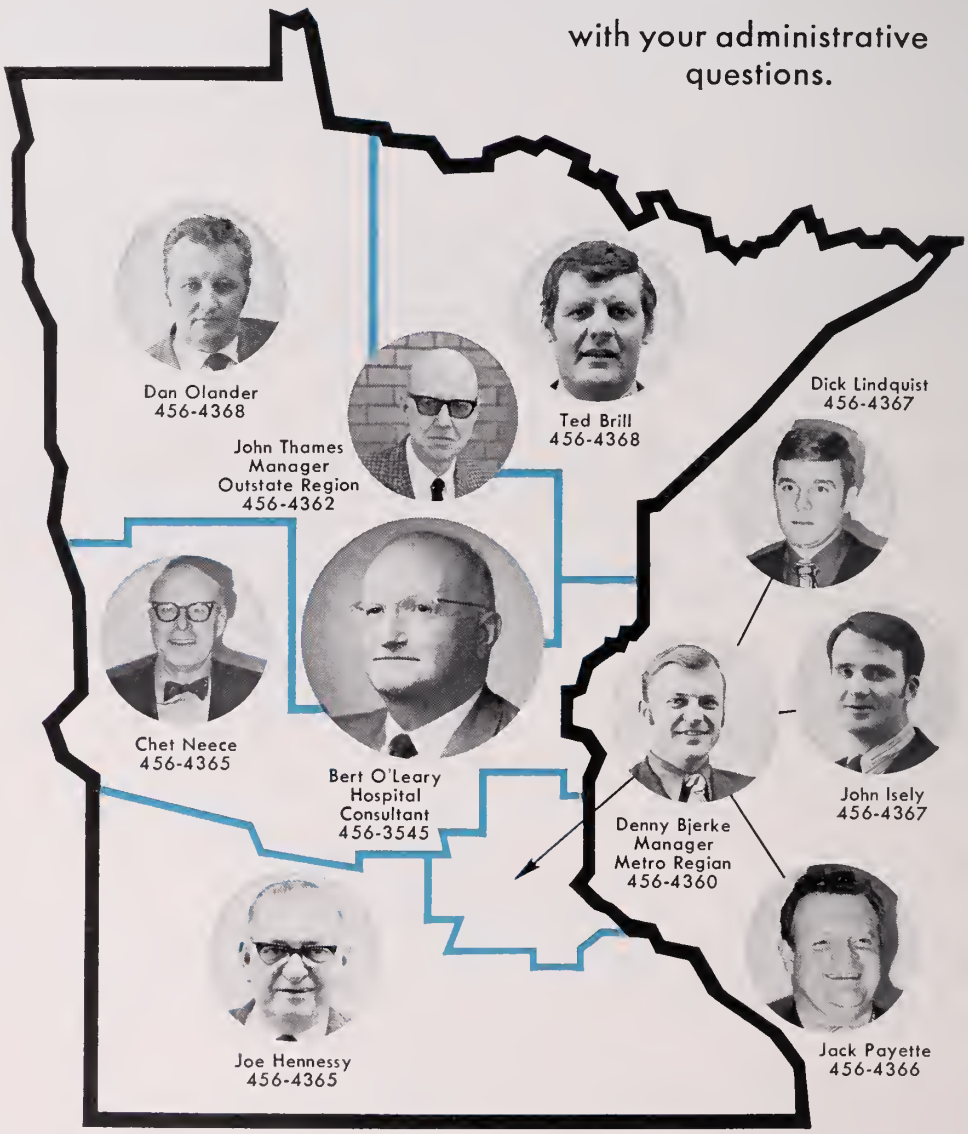
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President's Letter

There Is A New Specialist In Town

THE UNITED STATES of America is credited with having the greatest concentration of medical knowledge in the world today. Yet we in America are constantly in defense of our medical care and medical care delivery systems. Fragmentation of medical care in the last two decades has given rise to adverse criticism and allegations concerning the physician and the service that he renders.

The story is told of Mrs. Audrey Spencer, age 49, who saw her only doctor—an obstetrician—because of "headaches." In due course she was referred to a neurologist, internist, and finally to a psychiatrist who discovered that her headaches were the result of an emotional conflict within her family circle. The difficulty of entering into the available health care structure demonstrated by Mrs. Audrey Spencer gave rise to her concerned cry, "Is there a specialist interested in me and not my headache?" Yes, Mrs. Spencer, there is someone interested in you! There is a new specialist in town, a specialist in people. He is a general practitioner, the old family doctor, better trained in family problems and now being certified as the twentieth and newest of specialists.

The Diplomate of the American Board of Family Practice.

On this, the 25th Anniversary of the Minnesota Academy of General Practice, it is appropriate that we appraise our activities of the last 25 years before our medical community. It is appropriate that we introduce to our colleagues the twentieth and newest specialist, the Diplomate of the American Board of Family Practice. It is also timely to extend an open invitation to all of the medical community to assist us in providing more practicing physicians; to aid us in clinical teaching of our medical students; to improve the relationship among members of the medical profession, and to establish better public relations with our patients, so that they will understand the problems of physicians and the medical-care delivery system.

What have we in the Minnesota and National Academy of General Practice been about in the last 25 years? From the humble beginning of a group of interested Minnesota general practitioners who organized the Minnesota College of Physicians and Surgeons 25 years ago, in an attempt to preserve this discipline of medicine, there has evolved 51 state chapters, including chapters in Puerto Rico and the Virgin Islands. This represents a powerful organization known as the American Academy of General Practice, soon to be the American Academy of Family Physicians.

In the last two and one-half decades we can show some achievements that are now taken for granted but require an accounting for. *First,* we have become the second largest organized body of physicians in the world, numbering 32,000, second only to our parent organization, the American Medical Association. *Second,* we have defined family medicine as that organized body of knowledge or scientific discipline concerned with the comprehensive and continuing health maintenance of patients and their families. We have also defined the family physician as a licensed doctor of medicine who is responsible

(Continued to Page 728.)

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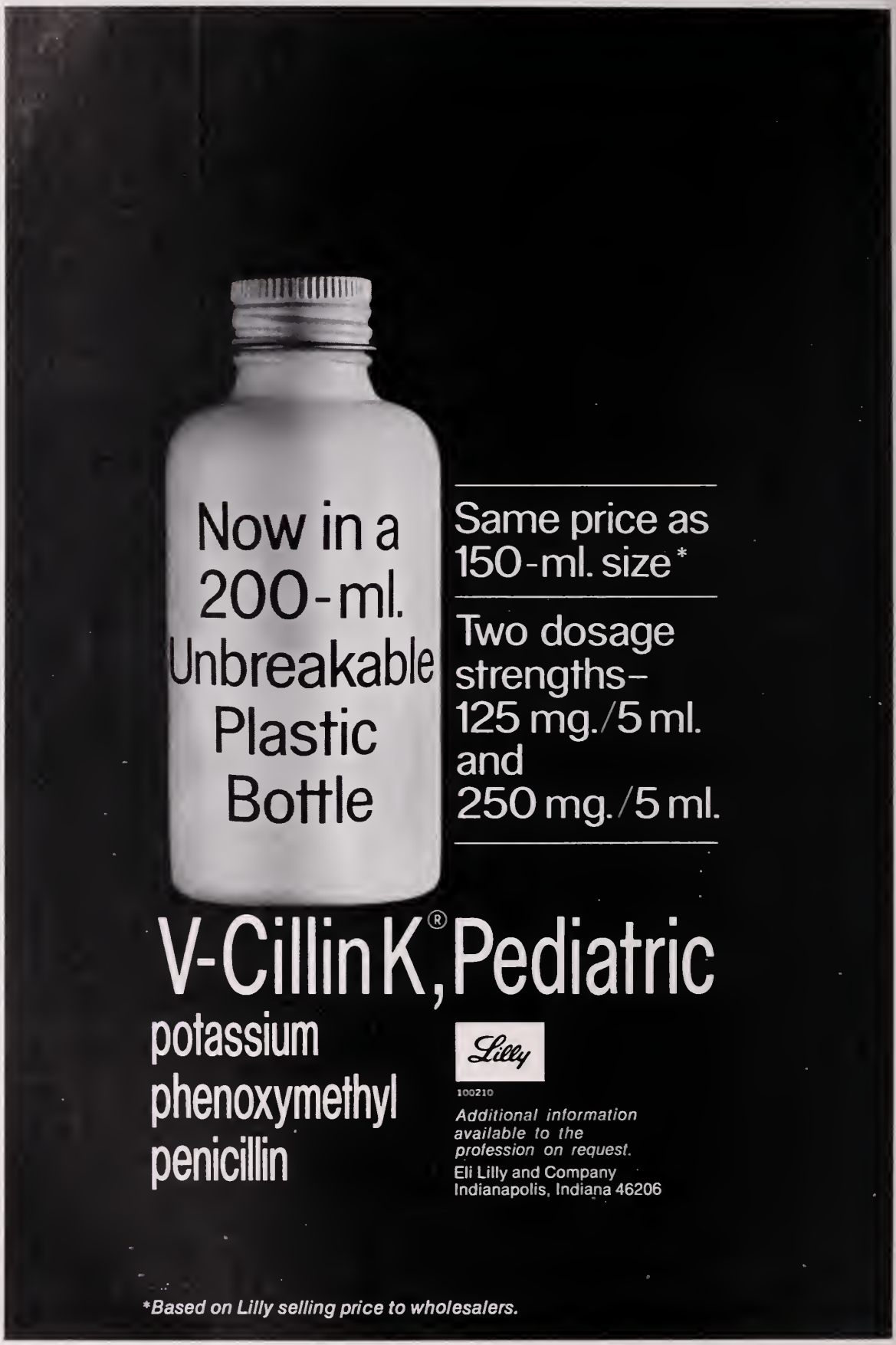
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Thorotrast-Induced Endothelial Cell Sarcoma of Liver*

RICHARD J. HOWARD, M.D.†, EDWARD P. TODD, M.D.†, RONALD H. DIETZMAN, M.D.†, AND RICHARD C. LILLEHEI, M.D., Ph. D.‡

THOROTRAST IS A 20-percent colloidal suspension of thorium dioxide that has been used in diagnostic radiology for angiography, hepatolienography, and for the visualization of body cavities. It was introduced into radiology in 1928 by Blühbaum, Frik, and Kalkbrenner[3] and was widely used as a contrast medium because it was nontoxic, did not cause vasodilatation, and did not elicit adverse immunologic reactions. Thorium dioxide, however, is a radioactive compound with a half-life of 1.39 x 10^{10} years. While it emits alpha particles, the decay products or "daughters" of thorium emit the stronger beta and gamma rays. In 1932 the A.M.A. Council on Pharmacy and Chemistry warned of the potential tumor-producing ability of thorotrast. Soon after, reports of thorotrast-induced carcinomas and sarcomas in rats, guinea pigs, and rabbits appeared,[10,11,21] and the use of thorotrast declined.

Since the first thorotrast-induced human liver neoplasm was reported by MacMahon, Murphy, and Bates[17] in 1947, over 100 tumors have been described following thorotrast administration. Dahlgren[7] has divided these tumors into three groups: (A) Tumors appearing at the site of injection; (B) tumors due to thorotrast deposited in body cavities; and (C) tumors due to systemic administration of thorotrast. In the first group are a fibroblast sarcoma of the neck six years after the administration of thorotrast for cerebral angiography,[18] and a chondrosarcoma of the axilla 22 years after injection of thorotrast into the axillary artery.[20] The subcutaneous deposit of thorotrast also results in dense granulomas ("thorotrastomas") which have caused progressive fibrosis and obliteration of the jugular and carotid vessels and damage to the cranial and sympathetic nerves of the neck.[2,4,15] One such case of a thorotrastoma of the neck causing obliteration of the common carotid artery and damage to the cranial and sympathetic nerves in the neck has already been reported from this institution.[15]

Included in the second-group tumors—those due to thorotrast deposited in body cavities—would be carcinoma of the maxillary sinus after instillation of the thorotrast into the sinus,[14] carcinoma of the breast after mammography,[5] carcinoma of the kidney after pyelography,[7] carcinoma of the bronchus after bronchography,[7] carcinoma of the ovary after salpingography,[7] and carcinoma of the eyelid after dacryocystography.[7]

When thorotrast is administered systemically, the thorium dioxide particles are taken up by cells of the reticuloendothelial system and deposited in the liver, spleen, bone marrow, and lymph nodes. Once deposited, elimination from the body is virtually negligible, thorotrast having a biologic half-life of approximately 400 years.[12] The interval between its administration and the discovery of tumors has ranged from three years, two months to 32 years, with most appearing 11 to 20 years after thorotrast injection.

Large series of thorotrast-induced hepatic tumors have been collected by da Silva Horta *et al.*,[9] da Silva Horta,[8] and Dahlgren.[6,7] Da Silva Horta *et al.*[9] traced 1107 patients who received thorotrast systemically between 1930 and 1952. Of 699 who had died, 25 had developed liver tumors including 22 hemangioendotheliomas, one bile duct carcinoma and two other types. In addition, 42 patients developed hepatic fibrosis. Dahlgren[7] collected 28 cases of hepatic neoplasms following thorotrast administration: 11 were hemangioendotheliomas or endothelial-cell sarcomas; nine were tumors of the bile ducts and eight were adenocarcinomas. Of the approximately 115 thorotrast-induced liver tumors reported thus far, two

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‡Professor of Surgery.

thirds have been sarcomas (hemangioendotheliomas), and one third have been hepatic adenocarcinomas and bile duct carcinomas.

Some authors still challenge the fact that thorotrast is carcinogenic, citing the rather small number of tumors considering the total number of systemic injections of thorotrast. Janower *et al.*[13] traced 153 patients who received thorotrast for cerebral angiography. None developed liver tumors, and there were only three tumors not related to thorotrast administration in the group.

Hepatic and splenic fibrosis can be found even more commonly than hepatic tumors after thorotrast injection. In the liver, fibrosis is seen around the portal spaces, adjacent to the central and hepatic veins, and under the liver capsule. Thorotrast granules are associated with these fibrotic areas. In the spleen there is progressive fibrosis until only a small fibrotic mass remains. Germinal centers may be almost completely obliterated and whorls of fibrous tissue may be all that remains of such centers.

The following case describes a liver tumor appearing 37 years after an intravenous injection of thorotrast.

Case Report

A 54-year-old female was referred to the University of Minnesota Hospitals on October 20, 1969, because of hepatomegaly and a filling defect in the liver seen on liver scan.

In 1932, 37 years previously, she had entered this hospital because of an increase in abdominal girth. On physical examination a mass, thought to be the spleen, was palpated in the left upper quadrant. Fifty ml of thorotrast were injected intravenously in order to visualize the spleen. Roentgen examination showed the spleen to be of normal size. At operation a 23-pound ovarian cyst was removed.

The patient had remained well until one month before admission when she went to her physician because of dysuria and low-back pain. Urinalysis showed bacteriuria, and she was treated with antibiotics for a urinary tract infection. On a followup visit one week later, she complained of an increase in the size of her abdomen. Examination in another hospital included a liver scan which showed hepatomegaly and an 8-cm filling defect in the right lobe of the liver. Needle biopsy revealed "a liver with thorium and secondary fibrosis." Bone marrow aspiration showed deposits of thorium with evidence of decreased erythropoiesis.

On admission to the University of Minnesota Hospitals she was noted to have a protuberant abdomen. A firm liver edge was palpated 8 cm below the right costal margin, extending to the left side of the abdomen. There was no fluid wave or abdominal tenderness, and bowel sounds were normal. Two 1-cm masses were located in the right antecubital fossa and numerous spider angiomata on the upper back and chest. She was not jaundiced.

Laboratory Studies

Initial laboratory studies were: Hemoglobin, 9.7 gm per 100 ml; white blood cell count, 8900 per cu mm; sedimentation rate, 90 mm per hr; reticulocytes, 7.2%; platelets, 220,000 per cu mm; alkaline phosphatase, 73 King-Armstrong units per 100 ml; serum glutamic-oxalic transaminase, 95 milli-international units per 100 ml; bilirubin, 0.8 mg per 100 ml; sulfobromophthalein retention, 27% after 1 hr; blood urea nitrogen, 13 mg per 100 ml; and creatinine, 0.8 mg per 00 ml. Urinalysis was within normal limits.

Chest x-rays and electrocardiogram were normal. Flat plate of the abdomen (Figure 1) revealed a lacy reticulated pattern in the liver and a small radiodense spleen. Several radiodense lymph nodes were also seen.

While in the hospital the patient developed ascites.

Laparatomy

On October 28, 1969, she underwent exploratory laparotomy. Approximately 4 liters of straw-colored



Fig. 1—Roentgenogram of the liver in a patient administered thorotrast 37 years previously. A lacy, reticulated pattern can be seen in the liver. The spleen is radiodense and shrunken. Many radiodense lymph nodes can also be seen.

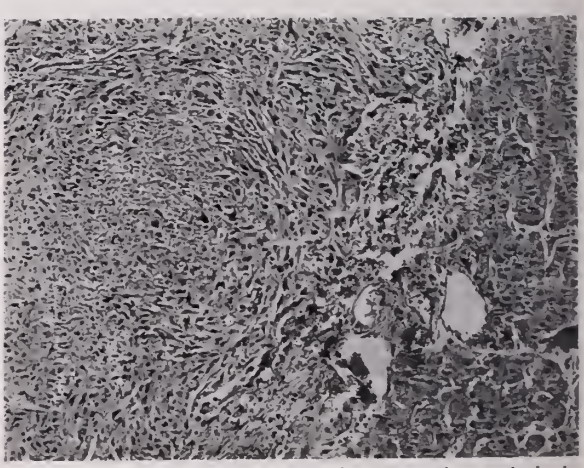


Fig. 2—Microgram of the liver showing relatively normal liver tissue (to the right) and tumor tissue on the left (60x).

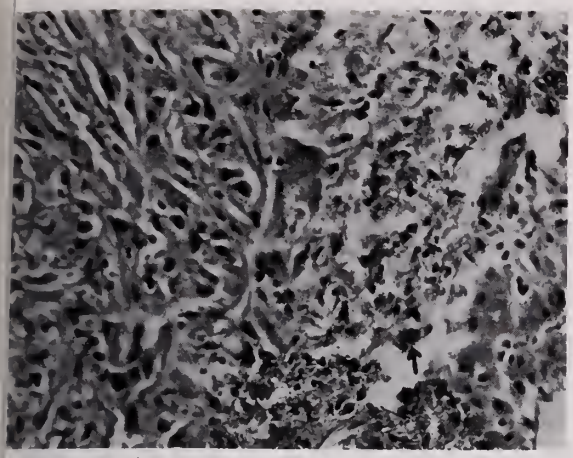


Fig. 3—Enlargement of section shown in Figure 2 Darkly staining thorotrast granules (arrow) can be seen at he margins of the tumor. (160x).

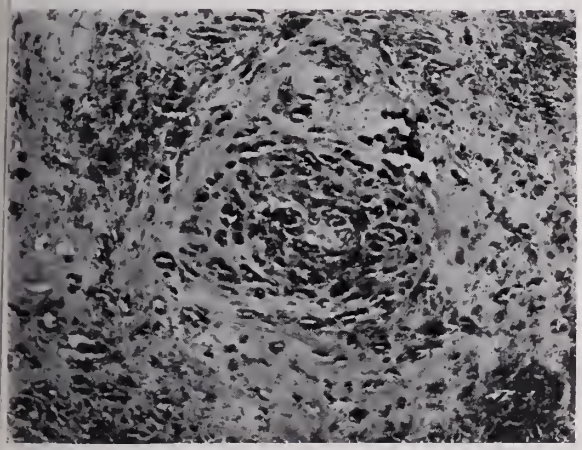


Fig. 4—Micrograph of the spleen showing intense fibrosis and complete obliteration of normal splenic tissue. Numerous deposits of thorotrast granules can be seen. (60x).

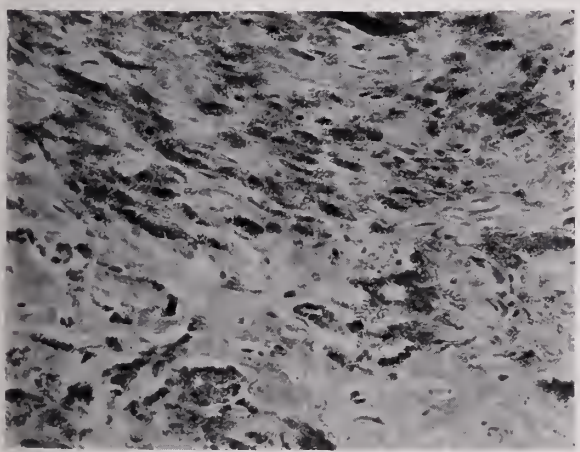


Fig. 5—Micrograph of a subcutaneous nodule showing fibrosis and abundant deposits of thorotrast granules. (160x).

fluid were removed from the abdominal cavity. The liver was coarsely nodular and firm; a large reddish-brown tumor mass occupied the right lobe. Biopsies were taken from different sites on the liver. The spleen was small, white, and extremely hard, and when a biopsy was taken the spleen did not bleed. One of the hard nodules in the right antecubital fossa was excised.

Postoperatively the patient had a progressively downhill course. She became jaundiced and the bilirubin rose to 11.2 mg per 10 ml. The serum glutamic-oxalic transaminase increased to 235 milli-international units per 100 ml. Renal failure accompanied the hepatic failure. The blood urea nitrogen rose to 74 mg per 100 ml and the creatinine to 4.2 mg per 100 ml. She died November 12, 1969. No autopsy was performed.

Histologic Examination

Histologic examination of the liver biopsy specimens showed a generally normal architecture (Figure 2). There was some fibrosis with enlarged portal spaces. Large collections of brownish pigment (thorotrast) could be seen in the portal spaces. Some sections showed a frankly malignant tumor (Figures 2, 3) thought to represent an endothelial cell sarcoma, characterized by intertwining bundles and sheets of elongated cells and fibers which formed distinct nodules. Pigment granules could be seen on the margins of the tumor (Figure 3).

Sections of the specimen from the spleen (Figure 4) showed heavily calcified hyaline scar tissue containing deposits of granular, brownish-gray pigment. Sections of the mass from the antecubital fossa (Figure 5) demonstrated similar hyalinized, calcified scar tissue with pigment deposits.

Discussion

The 37-year period between the administration of thorotrast and the discovery of the hepatic tumor makes this the longest latent period thus far recorded for a thorotrast-induced tumor. Ascribing the etiology of tumors to thorotrast depends on the previous administration, a sufficiently long latent period, and the discovery of thorotrast granules in close proximity to the tumor. This patient demonstrated many of the findings characteristic of previous administration of thorotrast. Subcutaneous granulomas were seen at the side of innoculation; fibrosis and calcification were observed in the spleen, and fibrosis and tumor were found in the liver. In all biopsy specimens thorotrast granules were abundant.

It is not possible to determine precisely the amount of radiation received by the organs in a patient given thorotrast, because the decay products differ chemically and are excreted at different rates from the parent thorium dioxide. The radiation from 74 ml thorotrast has been estimated to be between 1.5 and 8.3 rads per week to the liver and between 2.5 and 12.4 rads per week to the spleen.[16,18] Budin and Gershon-Cohen[5]

equated the alpha radiation emitted by 75 ml of thorotrast with that produced by 1.5 to 3 micrograms of radium. The patient here received 50 ml of thorotrast, the radiation dose after 37 years being between 2,886 and 15,969 rads to the liver, and between 4,810 and 23,858 rads to the spleen. Considering that the biologic effect for alpha particles is approximately 10 times that of beta and gamma rays when the radiation source (thorotrast) is intimately associated with the cells receiving it, the tissues in this case received a huge dose of radiation over the years.[15] For this reason it has been recommended that thorotrast not be given to anyone with a life expectancy of more than two years.[9]

Summary

A case is presented of a thorotrast-induced endothelial cell sarcoma with a 37-year latent period between the injection of thorotrast and discovery of the tumor. This patient demonstrated many of the pathological changes attributed to previous thorotrast administration, including granuloma at the site of injection, fibrosis of the spleen and liver, and a hepatic tumor.

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Health

As the doctor recovered, one thing was clear to him: health always depends on the ability to keep one's curiosity alive. There must always be something to look forward to as one goes to sleep at night. Each day must end with at least one question unanswered, one lesson yet to be learned. There must always be things that need one's individual care, whether they be plants or human beings. When he dressed and went to his office again, he was no longer afraid of retirement.*

*Walker Winslow, The Menninger Story

Thermography and Extracranial Cerebrovascular Disease

A New Method to Predict the Stroke-Prone Individual

T. D. CAPISTRANT, M.D.* and ROBERT J. GUMNIT, M.D.*

DURING THE PAST 20 years, much study has been devoted to the possible role of occlusion of the extracranial vessels in causing strokes. Evidence continues to accumulate in favor of the surgical restoration of patency to carotid vessels in selected individuals with transient or mild cerebral symptoms.[1] On the other hand, the natural history of occlusive disease of the internal carotid artery in asymptomatic individuals is relatively unknown. This important void in our knowledge of cerebrovascular disease exists because of a lack of a simple, safe and reliable test of carotid patency applicable to a large number of asymptomatic people. After more than a year's experience with infrared thermography, we believe it can serve as a satisfactory screening device.

Measurement of Infrared Energy

Thermography is performed with an infrared camera, originally developed by the Defense Department in 1953 and made available for medical use in 1956. An improved version of the camera was used in our work. It has a system of oscillating and rotating mirrors to scan the subject at the rate of 16 frames/second and to focus infrared electromagnetic rays (heat) onto a detector. The detector, in turn, converts variations in incoming infrared energy to electrical variations which are displayed on an oscilloscope screen. The resulting pictorial representation of temperature patterns is called a thermogram. The image is then photographed on polaroid film for a permanent record. Temperature differences of 0.1 degrees centigrade can be reliably detected; visually, they appear



Fig. 1—*Normal thermogram.* Marker to left at "5" indicates camera sensitivity is recording variations, in shades of grey, over 5 degrees centigrade between the warmest (white) and coolest (black) areas.



Fig. 2—*Abnormal thermogram.* Note the darker (cooler) area over the left forehead indicating reduced flow in the underlying skin vessels branches of the internal carotid artery. This patient had a severe left internal carotid stenosis.

*Department of Neurology, St. Paul-Ramsey Hospital, St. Paul, Minnesota.

Reprint requests to: T. D. Capistrant, M.D., Department of Neurology, St. Paul-Ramsey Hospital, St. Paul, Minnesota 55101.

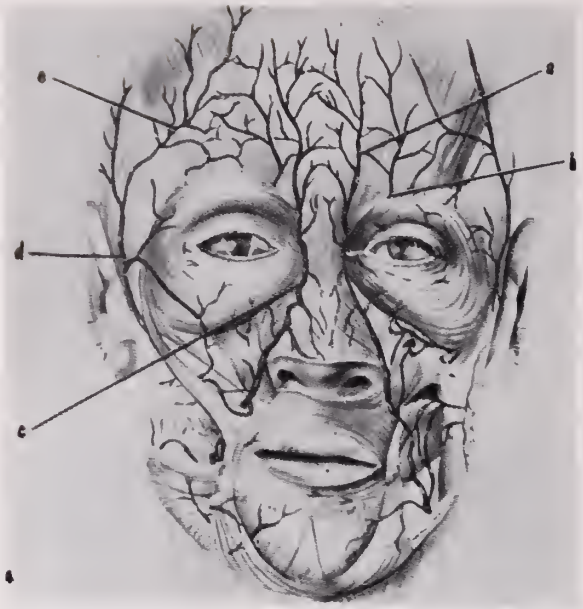


Fig. 3—Superficial Dissection of the Face: The medial supraorbital area on each side is supplied by the frontal (a) and supraorbital (b) branches (darker vessels) of the ophthalmic artery. Some anastomoses are present between the two sides, between the frontal and angular (c) arteries, and between the supraorbital artery and the frontal branch (e) of the superficial temporal artery (d). In spite of the anastomoses, the temperature of the medial part of the forehead is basically related to ophthalmic arterial flow; the collateral channels account only for minor variations in configuration of the dark patch of skin typically found by thermography in occlusive disease.

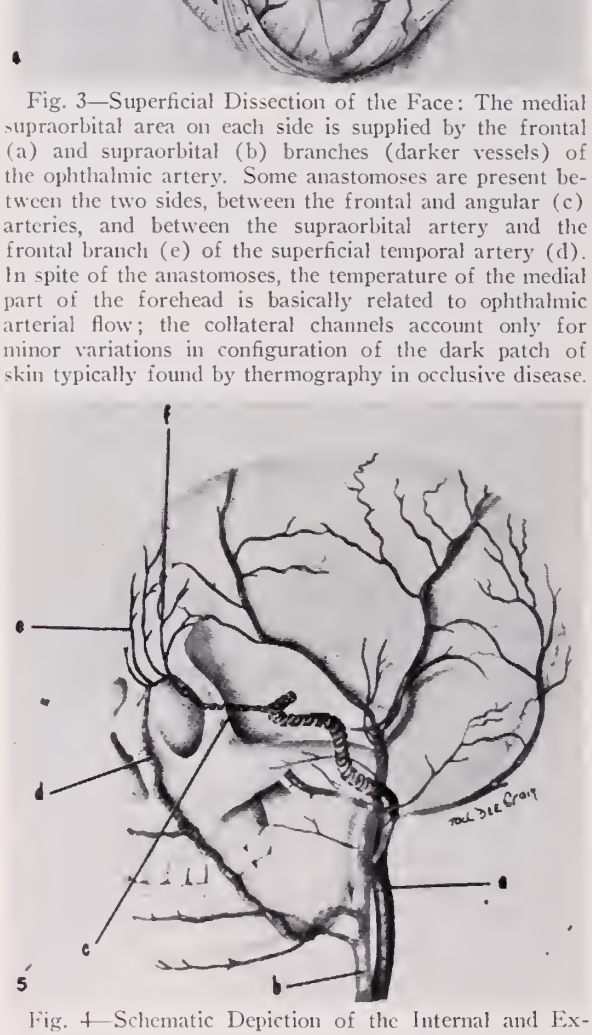


Fig. 4—Schematic Depiction of the Internal and External Carotid Arterial Systems: Blood flow in the frontal (e) and supraorbital (f) arteries (darker branches terminating outside the orbit) is dependent upon circulation in the parent ophthalmic artery (c). Connections to the internal carotid artery (a) and the angular branch (d) of the external carotid artery (b) are shown in relation to bony landmarks.

as variations in the shades of gray in th thermogram.

Applications of Thermography

Lawson published the first clinical observa tions using an infrared detector in 1956, dem onstrating increased heat in areas overlyin breast cancers.[2] Subsequently, other applica tions of thermography have been explored, in cluding diseases of the central nervous syste Despite the considerable literature on the sub ject, many areas remain unexplored or inade quately studied. In the field of neurologic dis eases, the most useful application of the too demonstrated thus far has been in the detectio of carotid occlusive disease: first described b Wood in 1964.[3] His studies indicated an 88 percent association between an "abnormal" thermogram and significant carotid narrowing. He found ipsilateral supraorbital forehead cool ing on the side of the stenotic occluded interna carotid artery. The cool areas are easily recog nized visually on the thermogram as "darl areas" (Figures 1 and 2). The cool pattern i these abnormal thermograms corresponds t the skin area supplied by terminal branches o internal carotid arteries via the ophthalmi branch. These anatomic vascular relationship are shown in Figures 3 and 4.* The internal carotid forehead skin branches are also demon strated in an unusual way in Figure 5: an in frared photograph obtained of a cadaver afte injection of warm water through a catheter inserted in the left internal carotid artery.

Methodology

Selection of Patients

The largest proportion of our study grou was an unselected number of patients under going cerebral angiography at St. Paul-Ramse and the University of Minnesota Hospitals. A small number of additional patients have bee obtained from the Minneapolis Veterans Hos pital, Hennepin County General Hospital an private practitioners.

Technique for Performing Thermography

The patient is given a brief explanation o the test and kept in a draft-free 70 degree Fahrenheit room for fifteen minutes. The cam

*Figures used with kind permission of E. Wood, M.D., and th Journal of Radiology.

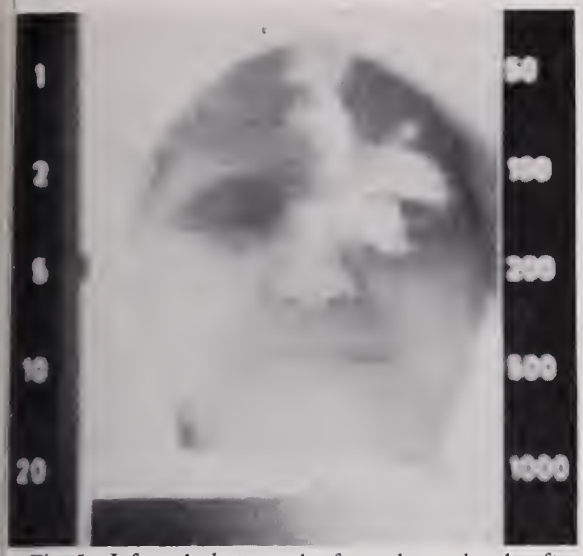


Fig. 5—Infrared photograph of a cadaver shortly after a warm water injection into the left internal carotid system. Note the warming (white streaks) corresponding to facial branches of the left internal carotid artery.

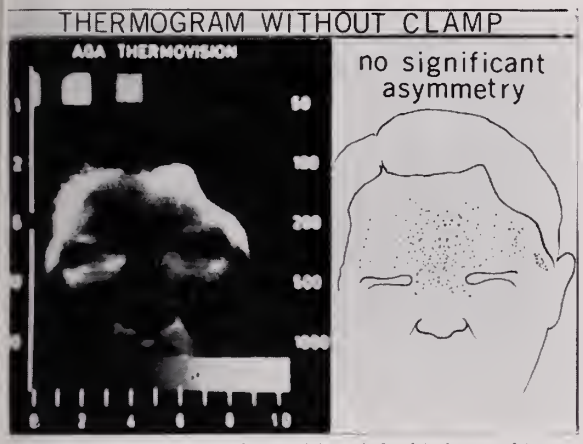


Fig. 6—This is a patient with a left-sided carotid narrowing showing no asymmetry of forehead temperature with standard thermographic technique.

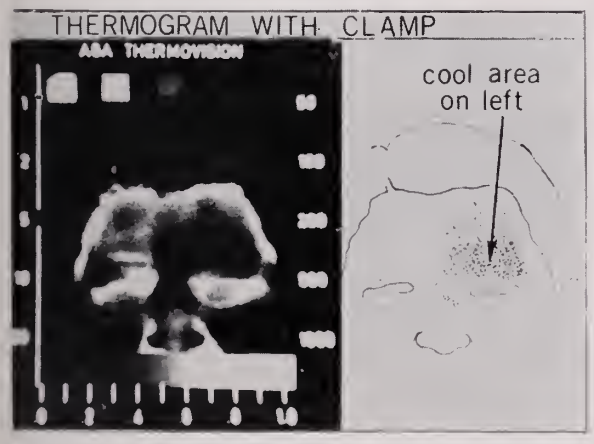


Fig. 7—After clamping of the superficial temporal artery for five minutes, a left-sided forehead cooling becomes apparent.

era (AGA Thermovision) scans both the subject and a reference temperature thermal gray scale simultaneously. A polaroid photograph is made of the oscilloscope screen. Next, a head-clamp apparatus is fitted over the patient with pressure pads positioned over the superficial temporal arteries. An adjustment is made causing the pads to obliterate superficial temporal artery pulsations bilaterally; and after five to ten minutes, another photograph is made. This is not uncomfortable and adds significantly to the number of positive correlations between thermography and internal carotid occlusive disease. The head clamp eliminates collateral flow from the external carotid circulation via the forehead which can obscure abnormalities in the internal carotid perfusion[5] (Figures 6 and 7). The thermal asymmetries are quantified by densitometric readings of the polaroid negative. The time for the entire procedure, excluding the 15-minute initial "wait period," is 10 to 15 minutes. The test is well accepted by the patients.

We regard a thermogram with a temperature difference of 0.7 degrees centigrade between medial supraorbital forehead areas as "abnormal." Significant internal carotid stenosis is considered to exist when 50 per cent of the vessel lumen in any projection is compromised (as visualized by angiography).

Results

As we have reported elsewhere, 201 controls and 181 patients were studied.[8] All patients had cerebral angiography, and in 95 of these cases adequate visualization of both carotid trees was accomplished. Thirty of these 95 cases had significant carotid stenosis (50-99%) or occlusions. "Standard" thermograms were abnormal in 57% of these cases while thermograms taken with the head clamp in place detected 83% abnormals.

Discussion

Although our results compare favorably with those of previous reports, it should be noted that these prior studies were done with what had been considered "standard" thermographic technique.[4,6,7] In our study, the standard techniques yielded only a 57-percent correlation rate between an abnormal thermogram and carotid stenosis.

Value of Head-clamp Provocative Test

The increase in sensitivity to 83 percent was achieved by use of the head-clamp provocative test. The lower yield of the standard techniques in our studies compared to previous reports results from our use of a relatively unselected patient population and the double-blind evaluation of thermograms and angiograms. We suggest that any future thermographic studies for internal carotid stenosis routinely include the head-clamp provocative technique.

Future Proposals

We plan to follow our pilot study with a screening program to include patients who have a relatively high risk of stroke: particularly individuals with hypertension, diabetes mellitus, coronary heart disease and peripheral arteriosclerosis. Yearly thermographic evaluation of such patients can serve two purposes. First, it would alert the physician, in the instance of a positive thermogram, to obtain a directed history and physical examination to see if the lesion was, indeed, asymptomatic. Secondly, one would obtain valuable information about the natural history of carotid occlusive disease and its relationship to subsequent stroke.

Acknowledgements

We wish to thank Dr. A. B. Baker, University of Minnesota Hospitals, Dr. Milton Ettinger, Hennepin County General Hospital, and Dr. Milton Alter, Minneapolis Veterans Administration Hospital for allowing us to examine their patients.

The authors acknowledge support from the U.S. Public Health Service (Contract HSM-110-69-37 and Grant No. NB 5364) and the St. Paul-Ramsey Hospital Medical Education and Research Foundation.

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Cover Photo

Dale E. Hammerschmidt, M.D.

Doctor Hammerschmidt, a resident in internal medicine at the Veterans Hospital, one evening around mid-night happen to be driving by Lake Harriet in Minneapolis and noticed the many pink clouds overhead. The lake itself was very still and glassy. It seemed as though all of creation was standing still for that moment.

He hurried home to get his camera, hoping that upon his return, this phenomena would not have changed. Upon his return, he found what he has captured on the cover photo . . . "Lake Harriet by Moonlight."

When we are flat on our backs there is no way to look but up.—Roger Babson

Threshold of Vibratory Perception in Normal Children*

MILTON ALTER, M.D., PH.D.† and MICHAEL BLAW, M.D.†

RELIABLE INFORMATION on the normal threshold of sensory modalities mediated by the posterior columns of the spinal cord would be very useful in the neurological evaluation of children when posterior column impairment is suspected. In the present study, vibratory threshold was investigated in a group of normal children.

Subjects and Equipment

A group of 77 normal children attending a public school or a private nursery school was studied. The children ranged in age from four to 12 years with approximately equal numbers of boys and girls in each age group.

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†From the Neurology Service, Minneapolis, Veterans Hospital the University of Minnesota, Minneapolis, Minnesota, and the Department of Pediatrics and Neurology, Southwestern Medical School, Dallas, Texas.

A Bio-Thesiometer was used to measure vibration threshold. This instrument is electrically driven and delivers a precisely controllable vibratory stimulus tangentially to the skin at 120 cycles per second. The amplitude of the stimulus, graded in vibratory units calibrated in microns of motion, is read from a dial.

Technique

The test was described briefly and the sensation delivered by the Bio-Thesiometer was demonstrated to each child. The sites of testing were the dorsum of the right toe behind the nail and to the ball of the right index finger. The child sat in a chair with the limb resting on a cushioned pad. Six trials were used at each site. On the first three trials the threshold was determined by stimulating from zero to

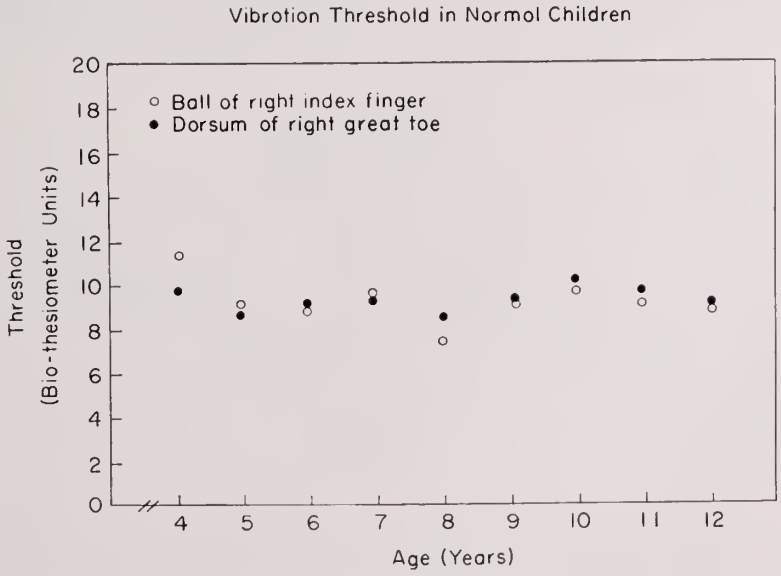


Fig. 1—Vibratory perception threshold in normal children

the first perceptible vibratory sensation and, on the second three trials, by stimulating from well above the threshold to the least perceptible stimulus. The threshold of vibratory perception was defined as the mean of the six observations at each site.

Results

In Figure 1, the threshold of vibratory perception is shown for ages four through 12. The fitted line for these observations does not differ significantly from a straight line parallel to the abscissa at nine Bio-Thesiometer units.

No difference in threshold was found between boys and girls; moreover, no consistent difference in threshold was found between toe and finger. The threshold was generally slightly higher when measured from a stimulus well above threshold to the least perceptible stimulus than when zero stimulation to threshold stimulation was used.

Variability was small and rarely exceeded three vibratory units indicating reproducibility of the tests. The children appeared to enjoy the test and cooperation was excellent.

Discussion

The results of the Bio-Thesiometer test show that vibratory threshold may be measured accurately and reliably in children as young as four years. The test affords greater sensitivity and precision than can be obtained with a tuning fork and can therefore be applied to children whenever posterior column impairment is suspected.

Under the conditions of the test, the threshold of vibratory perception was constant over the age range examined. It was essentially the same at finger and toe and for both sexes. The similarity in vibratory threshold between the sexes has been reported previously[1] although others[2] found a higher threshold for males than females. Curves of vibratory threshold plotted against age published by Mirsky and associates[1] imply that threshold increases in linear fashion with age and increases at a greater rate in the lower than the upper extremity. However, only a few individuals under 10 years of age were included in their study. In a more recent report, Steiness[2] also found a linear relationship between age and vibratory thresho'd, but he had no observations in individuals under 10 years of age (Figure 2).

Our data suggest that the vibratory threshold when plotted against age may be nonlinear, the upward break in the curve occurring sometime beyond 12 years of age. Our results also suggest that any consistent difference in threshold between fingers and toes is not to be regarded as normal under 12 years of age.

Speculation

Vascular Factors

Pearson[3] postulated that change in vibratory threshold with age was attributable to vascular factors and he cited anatomical evidence of poor

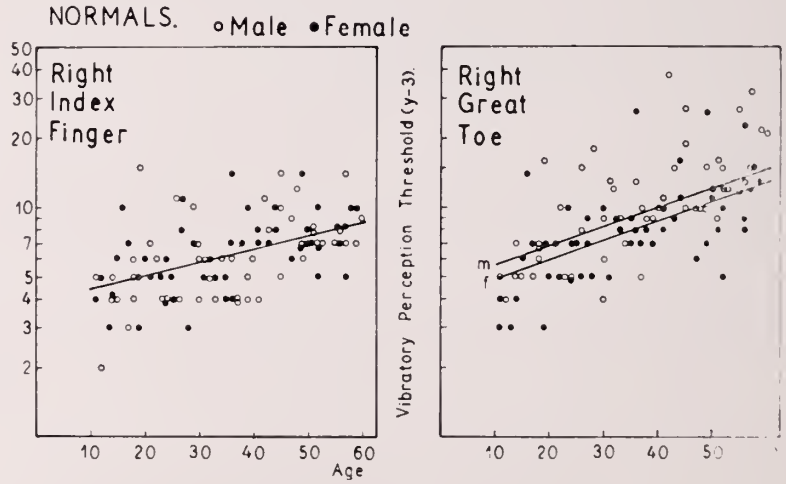


Fig. 2—Vibratory perception threshold in a normal population according to I. Steiness (1957).

blood supply to the column of Goll in the thoracic region.

Vitamin E Deficiency

Sung[4] correlated pathological evidence of neuroaxonal dystrophy with age in nucleus gracilis and cuneatus. He did not find this anatomical change in patients under 20 years of age except in those with cystic fibrosis or congenital biliary atresia. He postulated a relationship between vitamin E deficiency and neuroaxonal dystrophy, citing experimental evidence that prolonged vitamin E deprivation results in neuroaxonal changes similar to those seen in humans. Since vitamin E is fat-soluble, deficiencies can occur in patients whose fat absorption is abnormal, i.e., in cystic fibrosis or congenital biliary atresia. The pathological changes in nucleus gracilis and cuneatus may be related to abnormalities in vibratory threshold because these nuclei subserve the posterior columns which mediate vibratory perception. If the pathological changes Sung described are related to the increase in vibratory threshold with age, then one would expect vibratory threshold not to increase with age before age 20. Our data which show the threshold of vibratory perception to be constant until at least 12 years of age are compatible with the thesis that the increasing threshold of vibratory perception with age may be related to vitamin E deficiency.

Bio-Thesiometer is the vibrometer model manufactured by Electro-Medical Engineering Company, Burbank, California.

Summary

Vibratory threshold at the finger and toe was investigated in 77 normal children ranging in age from four to 12 years.

The threshold was essentially constant over the age range examined. No significant difference in threshold was found between sexes, and there was no significant difference between finger and toe.

Heretofore, the slope of the vibratory threshold curve has been regarded as increasing with age and increasing more rapidly in the lower than in the upper limb. The present study showed that the curve may be unrelated to age in early life. An upward break indicating progressive elevation of the vibratory threshold with age apparently occurs sometime after 12 years of age, possibly around age 20.

Acknowledgments

The authors would like to acknowledge the help of Mr. B. M. Nelson, superintendent of Brimhall Elementary School, Roseville, Minnesota. Dr. J. H. Sung and Dr. M. Stadlan offered helpful suggestions.

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Healing

As a surgeon, I am sometimes called upon to cut away the ureter and to implant it into another part of the bladder. When my work has been completed I am ashamed of its crudity. Compared with the job done by a plumber, my joint is a poor and botched concern. Yet when I examine it a year after, I am scarcely able to tell which is Nature's joint and which is my own. Some intelligence in the patient's body has made good my failure, paring off redundant tissue here, adding new tissue there, until perfection has been attained. Does that intelligence exist only in the brain? No, for if I divide all the nerves that reach that spot from the brain, the work is performed just as well. If we concede intelligence to the body, we must also concede to it some degree of consciousness.*

*Kenneth Walker, The Diagnosis of Man

To himself every one is an immortal; he may know that he is going to die, but he can never know that he is dead.—Samuel Butler

From The Doctor's Dream*

I had a dream, and in that dream
I thought that I had passed
Into the realm of blissful rest
That doctors reach at last.

I dreamed of all the ups and downs
Of thirty years of practice,
That brought with many a scented rose,
Its compensating cactus.

About the doctors and their bills,
The good and bad we did.
The lives our skill so often saved,
Mistakes the earth had hid.

The strictures on our moral worth,
The sins we do commit,
And universal dump we get,
By wholesale in the pit.

For many hold 'twould be so hard
Through Heaven's gate to wheedle
A doctor as to drive a camel through
A hypodermic needle.

Yet in my dream there seemed to be
Misapprehension here;
For I felt sure physicians will
Among the saints appear.

For from the fount from whence they're cleansed,
E'en doctors may come clean;
God gives to no exclusive class
The power to enter in.

And thus I dreamt that round me stood
The victims of disease,
The patients I had failed to cure,
Though some had paid my fees.

One said, "It is a happy place,
My bliss is unalloyed;
Through your mistakes just ten years more
Of Heaven I have enjoyed."

Another made this queer complaint;
"I'm prematurely sent;
The bungling doctors got me here
Before development.

"I'm filled with love, my joy overflows,
But what I most regret,
On earth I should have stayed and got
Capacity for it."

I here got shaky in my shoes,
And asked if they'd attack us,
And raise a rumpus in these courts,
With questions of malpractice.

"Oh, no!" he said, "there's no redress,
No righting this affliction:
For courts are not in session here
For want of jurisdiction.

"And if they were, in our behalf
We must ourselves appear;
A first-class lawyer can't be had,
I never found one here."

---

*William Snowden Battles (1827-1895) studied medicine under Dr. Timothy Hunt Baker at Millbrook, Ohio, for four years. He received the degree of Doctor of Medicine in 1852 at Starling Medical College in Columbus, Ohio. His contributions to medical literature are studies on scarlatina, ergot and alcohol. His research and writing brought him the vice-presidency of the Ohio State Medical Society in 1886 and other honors.

There may be splinters on the ladder of success but you don't notice them unless you are sliding down.—Bert Lawlor, quoted in Forbes

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A man is like a tack; he can go only as far as his head will let him.—Construction Digest

Obvious Seizures from Carbenicillin

PAUL BLUM, M.D.* and JOHN M. MATSEN, M.D.

THE NEUROTOXICITY and epileptogenic properties of penicillin have been recognized since 1945.[1-4] More recently reports have appeared describing seizures associated with "massive" intravenous penicillin G therapy,[5-7] with administration of large doses of intravenous penicillin G to patients on cardiopulmonary bypass,[8,9] and to patients with uremia and compromised renal function.[5-7,10-12] That the newer, semisynthetic penicillins have the potential of epileptogenicity has also been reported when massive doses have been given in experimental situations,[13,14] although little has been reported about actual seizure events in humans.[15]

This paper describes the occurrence of generalized seizure activity in a uremic child treated with carbenicillin and reports the incidence of central nervous system adverse effects with carbenicillin, a new semisynthetic penicillin used at times in very large doses because of activity at high levels against many strains of *Pseudomonas aeruginosa.*

Case Report

The patient, an eight-year-old child, was apparently well until early February 1969 when she experienced a major motor seizure. Evaluation by her family physician revealed a normal physical examination and a normal laboratory workup with the exception of a blood urea nitrogen of 115 mg%, the finding of which prompted further study: a massive bilateral low pressure reflux was observed, on a voiding cystogram.

Physical and Bacteriologic Findings

Upon admission to the University of Minnesota Hospitals for further evaluation examination disclosed a low-grade fever and right costovertebral angle tenderness. Her neurological examination was within normal limits. Admission laboratory findings included a blood urea nitrogen of 178 mg%, and a creatinine of 10.1 mg%. Her hemoglobin was 7.2 mg% and her creatinine clearance only 4 cc/minute. Greater than 100,000 colonies per ml of *Escherichia coli* were demonstrated on urine culture. Studies done to explore the anatomical state of the patient's kidneys and collecting systems revealed congenitally hypoplastic kidneys. Ampicillin, given over a course of 14 days, cleared the *Escherichia coli* from her urine and rendered the child afebrile and asymptomatic. Catheter drainage of her bladder was instituted and her blood urea nitrogen and creatinine fell to levels of 72 mg% and 8.1% respectively and remained constant.

In early April catheter drainage was discontinued when the child complained of right flank pain. She was febrile at this point. Urine cultures grew out *Pseudomonas aeruginosa.* A course of polymyxin B thereby failed to eliminate the organisms from the child's urine, but she again became asymptomatic and afebrile. The blood urea nitrogen and creatinine rose again to 96 mg% and 12.5 mg% respectively.

Carbenicillin Therapy

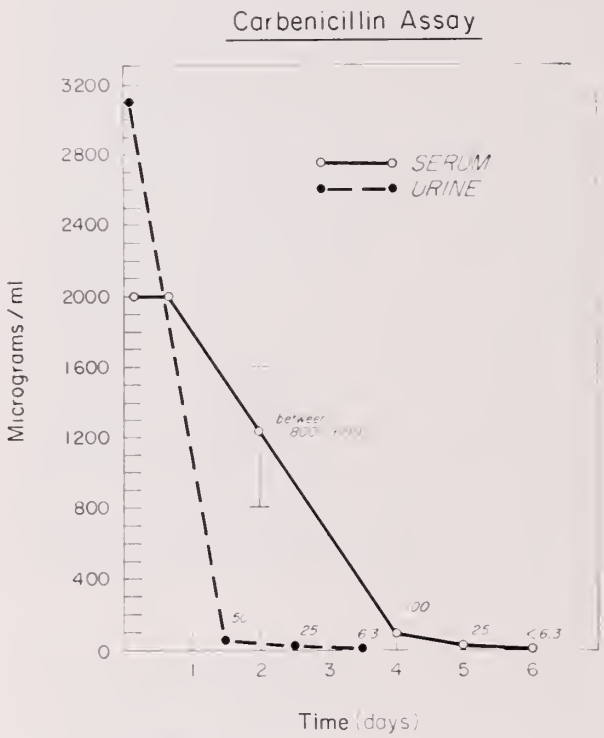
In late April a third episode of right flank pain, fever to 103° F, suprapubic tenderness and a urine culture which continued to demonstrate *Pseudomonas aeruginosa* led to the decision to use gentamicin and carbenicillin in attempting to clear the *Pseudomonas* from the urinary tract. Accordingly the child was given a single intramuscular dose of 33 mg gentamicin in view of her creatinine clearance of 4 cc/min. She was also started on 650 mg carbenicillin every three hours intravenously. This dosage was approximately 250 mg/kg/day, *or one-half the recommended maximum dose* of 500 mg/kg/day in children and was felt to be consistent with dosage recommendations for semisynthetic penicillins in patients having renal disease.[16] But subsequently it was considered high in view of the report of the extension of the half-life of carbenicillin in patients with renal failure.[17] The patient gradually became afebrile and her symptoms decreased.

Toxicity

After five days on this regimen the child experienced a generalized convulsion, which was followed by a second convulsive episode 12 hours later. Laboratory data revealed a serum sodium of 140 meq/L, potassium 5.7 meq/L, calcium 5.7 meq/L, chloride 95 meq/L and bicarbonate 24 meq/L. The blood urea nitrogen was 66 mg% and the creatinine 7.9 mg%. Serum magnesium was 1.5. Hemoglobin was 6.6 mg% and a white blood count

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9700 mm³ with a normal differential count. Her blood pressure just prior to and immediately after the seizures was normal. Urine cultures were sterile. Carbenicillin therapy was discontinued, and serum levels were drawn that day and for the following eight days. A serum level of 2000 micrograms per ml was obtained on two separate determinations, each from serum taken at the time of a seizure episode. Results of the child's serum and urine carbenicillin levels and their fall-off are expressed in the Figure.



Figure—Assay of carbenicillin in the serum and urine of the patient.

The patient's level of consciousness returned to normal and no further seizure activity was noted. In late June, 1969, she received a renal homotransplant from her mother. Since that time she has done very well.

Discussion

It is quite apparent that many factors may have caused or contributed to the two seizures in this patient. Since carbenicillin contains 7.3 meq of sodium per gram, excessive sodium may have contributed to an electrolyte imbalance; yet electrolyte imbalance seems to be ruled out by laboratory studies obtained after the first episode and well before the second. An infection of the urinary tract was being treated but the child had become asymptomatic and afebrile when the convulsions occurred. Careful continual monitoring of blood pressure revealed no reason to suspect any sudden hypertensive episodes contributing to a possible encephalopathy. Uremia may have been an underlying factor; however, the child had tolerated comparable or higher blood urea nitrogens before the seizures occurred. Furthermore, these elevated levels were tolerated well for another two months. A probable lower seizure threshold would seem evident, however, from the fact that, three days post transplant surgery in late June, 1969, she again experienced a major motor seizure. At that time she was dehydrated (3 kg weight loss in 36 hours), febrile (101°), with a blood pH of 7.3, and a serum sodium of 151 meq/L. She has had no seizure episodes in the subsequent nine months.

Transport from Cerebrospinal Fluid

Pappenheimer and co-workers[18] demonstrated the presence of a mechanism for actively transporting certain organic acids out of the cerebrospinal fluid. Fishman[19] showed that penicillin excretion from the cerebrospinal fluid is also inhibited by the presence of phenolsulfonphthalein and aminohippuric acid. His date support the existence of a transport system, which he presumes is in the choroid plexus and actively transports organic acids from the cerebrospinal fluid. It may be analogous in function to the proximal renal tubule.

Possible Neurotoxicity

The references previously cited suggest the possibility of neurotoxicity when large doses of penicillin are given to patients with compromised renal function.[5-7,10-12] In the uremic state of this patient, there would be a build-up of many organic acids. It is probable that they contribute to an increased level of carbenicillin in the cerebrospinal fluid. It is unfortunate that permission was not obtained for performing a lumbar puncture to obtain cerebrospinal fluid for carbenicillin analysis in this patient. The probability does exist that this child, who had originally presented with a generalized convulsion in February 1969, has a significantly lowered seizure threshold. The electroencephalograms obtained during and following the episodes in late April, however, failed to reveal any persistent seizure focus. We feel,

therefore, that markedly elevated blood levels of carbenicillin most likely precipitated the seizure episodes experienced by the patient while on the carbenicillin therapy.

Compromised Renal Function

Robinson reported a patient in whom twitching and mental confusion were associated with blood carbenicillin levels of 800 mg/ml;[20] his studies also indicate that carbenicillin passes into the cerebrospinal fluid only with difficulty. The recommendation is made[21] that treatment of meningitis with carbenicillin requires intraventricular or intrathecal administration of the antibiotic, and studies[22] have shown that cerebrospinal fluid levels as high as 1,070 μg/ml have been well tolerated. To date, 481 patients in the United States have been reported treated with a total of 508 courses of carbenicillin. Of these, there have been six instances of central nervous system irritability, with three cases (not including the present reported case) of major motor seizures. All six instances of central nervous system stimulation have occurred in patients with compromised renal function.[23]

Monitoring of blood levels of carbenicillin may be advisable in patients with compromised renal function receiving large intravenous doses of this antibiotic, especially in patients known to have a history of major motor seizures. The potential for neurotoxicity should also be recognized in administering carbenicillin by the intrathecal or intraventricular route.

Acknowledgement

The cooperation of the staff of the Diagnostic Microbiology Laboratories of the University of Minnesota is gratefully acknowledged.

Generic and Trade Names of Drugs

Disodium α carboxylbenzylpenicillin (carbenicillin)—Pyopen. (Beecham) and Geopen (Roerig).

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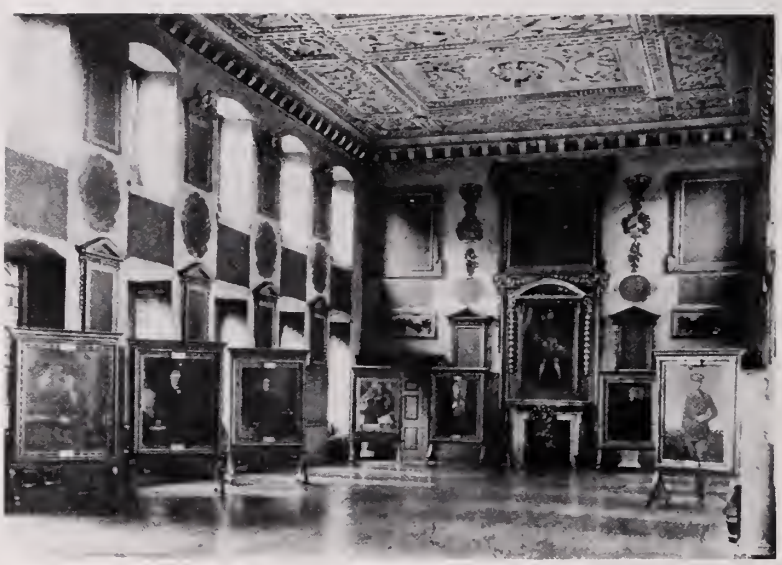
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Conceit may puff a man up, but never prop him up.—Ruskin

Historic Hospitals

The Community of St. Bartholomew's



The Great Hall of St. Bartholomew's Hospital, London. Courtesy National Library of Medicine, Bethesda, Maryland.

A hospital is many things: treatment center for the sick, technical school, laboratory of clinical research, and community of health workers. The fame of history's great hospitals, however, rests in large part on their communities of physicians. Prominent examples include Guy's, the Allgemeines Krankenhaus, Johns Hopkins, and many others which come to mind.

Pictured is the Great Hall of St. Bartholomew's Hospital in London. Among the many portraits of famous physicians associated with the hospital are those of Pott, Abernathy, Charles Bernard, Paget, and William Harvey. The impressive list of those immortalized by important discoveries, insights, and descriptions must be supplemented by a longer list of less well known men of great organizing power and general ability. The latter group has been as important as the former in raising the hospital to the position it occupies in the esteem of the world.

Communities of outstanding physicians elsewhere, past and present, have provided the mutual support and stimulation which have resulted in major scientific developments and improved clinical medicine. The modern phenomenon of medical specialization rests entirely upon the concept of community. Group practice is its logical outgrowth.

Magraw has pointed out that hospital staffs not only have determined the character of modern hospitals, but through the informal sense of community and formal systems of peer review have replaced governmental licensure as the most effective means of quality control in medical practice.

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Teenage Mothers

A Pediatric and Obstetrical Group At High Risk

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In recent years it has become apparent that the number of teenage mothers is increasing.[27,34] Specifically, the number of mothers less than 16 years of age is increasing. This fact becomes important because of the generally poor medical and social outcome resulting from these pregnancies.[3,6,7,32] However, a review of the obstetrical literature dealing with these women has not until recently emphasized the generally high-risk nature of this group of patients. No study in the literature has stressed follow-up of these women and their babies nor dealt with prevention of future pregnancies in this group of patients. It is only through recognition of the problems unique to these women that comprehensive and completely adequate programs can be designed to meet their specialized needs. In order to determine the variables which characterize the teenage mother and to determine if her needs are being met, a retrospective study of all teenage pregnancies occurring at the Hennepin County General Hospital during 1968-1969 was undertaken to better understand this group of obstetrical patients. The results of this study together with a review of the literature are presented in this paper.

Methods

The study group consisted of all pregnant females who were age 16 or less at the time delivery occurred. The period of study was the years 1968 and 1969. The study represents a pilot summary, rather than definitive data that can be extrapolated to other institutions.

Results

Incidence

Table 1 shows that in 1968 through 1969 120 deliveries occurred to girls aged 16 years or less. This represents 4.4% of the total deliveries at Hennepin County General Hospital.

TABLE 1

Hennepin County General Hospital (1968-1969)
Identification Data

Total Deliveries	2720
Deliveries—16 years or less	120

4.4% of Total Deliveries

Epidemiologic Data.

Of special note is the fact that 26% of the girls are married and that only 20.9% are Negro (in contradition to previous studies concerned with teenage pregnancies) (Table 2).

TABLE 2
Hennepin County General Hospital (1968-1969)

Identification Data

	Number	Percentage
Age:		
16	80	66%
15	30	26%
13-14	10	8%
Married:	32	26%
Gravida 2:	10	8%
Race:		
Caucasian	93	77.5%
Negro	25	20.9%
Indian	2	1.6%

Prenatal Care.

The Hennepin County General Hospital clinic is a standard obstetrical clinic. These girls received no special or high-risk treatment unless a medical indication (diabetes, toxemia, etc.) was present. Deaconess is a home for unwed mothers run by Lutheran Social Service.

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All girls from Deaconess received prenatal care at that institution, and were delivered at Hennepin County General Hospital only if their pregnancy became classified as "high-risk" due to medical indications. Maternal and Infant Care clinics are those run by the Children's Bureau and all Maternal and Infant Care patients deliver at Hennepin County General Hospital regardless of the medical status of their pregnancy (Table 3).

It should be noted that only 11% of the girls receive any form of social-emotional counseling as indicated by their medical charts. Furthermore, most of the social-emotional notations concerned gross psychiatric deviations. In no case was a comprehensive approach to the patient indicated on her chart.

TABLE 3
Hennepin County General Hospital (1968-1969)
Prenatal Care

	Number	Percentage
Hennepin County General Hospital	66	55%
Maternal and Infant Care	28	23%
Deaconess	11	9.5%
None	15	12.5%

14 (11%) have a social-emotional notation on chart.
11 (9.5%) received prenatal care at Deaconess, and presumably received social and emotional counseling.

Maternal Complications

The 7.5% C-section rate is contrasted to the overall incidence of C-sections in this institution of 4.2% (Table 4). The incidence of toxemia (18.3%) is comparable to other similar studies. However, the incidence of prolonged labor (16.6%) premature rupture of membranes (16.6%) and postpartum hemorrhage (11.6%) is higher than generally found in the literature.

TABLE 4
Hennepin County General Hospital (1968-1969)

Maternal Complications:

Complication	Number	Percentage
Toxemia	22	18.3%
Prolonged Labor	20	16.6%
C-Section	9	7.5% (4.2%)
G.C./VDRL (+)	9	7.5%
Premature Rupture Membrane	20	16.6%
Postpartum Hemorrhage	14	11.6%

Fetal and Neonatal Complications

The rate of prematurity (14%) was expected (Table 5). The fact that 25% of these babies are placed in our high-risk infant nursery has implications for the pediatrician and will be dealt with in the discussion section. The incidence of sepsis (8.3%) may reflect the high incidence of premature rupture of the membranes found in our mothers. The perinatal death rate (2.5%) compares favorably with other similar series.

TABLE 5
Hennepin County General Hospital (1968-1969)

Fetal and Neonatal Complication

Complication	Number	Percentage
Prematurity	17	14%
Intensive Care Unit	30	25%
Sepsis	10	8.3%
Lungs	4	3%
Perinatal Death	3	2.5%

*(One baby arrived DOA: age six months)

Follow-Up Care

In order to be considered as utilizing family planning services (44%) a mother had to demonstrate usage of a contraceptive technique and/or have received a device at her six-week postpartum visit (Table 6). Of the mothers who kept their babies (74.3%), adequate follow-up (26%) consisted of regular visits to the Pediatric Clinic. Sporadic follow-up (28%) is defined as episodic emergency room care and no follow-up (46%)

TABLE 6
Hennepin County General Hospital (1968-1969)

Follow-up:

	Family Planning	Percentage
Mother:	53	44% of Total 65% Hennepin County General Hospital Responsibility
	Mothers Keep Baby	Percentage
Baby:	87	74.3%
No Follow-up	40	46%
Sporadic Follow-up	24	28%
Adequate Follow-up	23	26%

curred when the baby was not seen again.

efore and After 1960

Table 7 summarizes data available before 960 and the studies of the early 1960s, analyzed ith regard to only those teenagers who were 16 ears of age or less. It should be noted that al- hough the perinatal loss has been lowered re- arkably, the incidence of toxemia and prematu- ty remained uncomfortably unchanged. This eems to indicate that more babies of high-risk regnancies were being salvaged, but no significant nprovement was being made in lowering the in- idence of complications of pregnancy. No data egarding morbidity is offered. The problem be- omes more apparent when the overall United tates statistics concerning perinatal mortality are aken into account. In 1965 the expected United States rate of prematurity was 8.2% while the verall infant mortality was 24 per 1000 live irths.[1] Clearly, this group of young women was over-contributing to perinatal mortality. It s assumed that because of the high rate of rematurity, significant infant morbidity was lso developing from the group of young mothers.[1] However, because of the lack of ade- quate follow-up in the babies, the question of infant morbidity remains unanswered.

TABLE 7
Summary of Data
Summary of Studies on Young Primiparas II—

A. Total Number of Patients Before 1960: 5960
   Total Number of Patients After 1960: 1089
B. Large Variation in the Percentage of the Total Obstetrical Service.
C. All Girls Between 12 and 16 Years of Age.
D. 81% of Girls are Unmarried.
E. Large Variation in the Number of Negroes Studied; Number of Primiparas Studied.
F. Little Definition of What Is Meant by Adequate Prenatal Care.
G. Complications:

	Before 1960	After 1960
Toxemia	14.4%	15.7%
Prolonged Labor	8%	Data Not Adequate
C-Section	1.5-3.0%	Data Not Adequate
Prematurity	13.7%	13.6%
Perinatal Loss	42.8/1000	27.5/1000
Post-Partum Hemorrhage	2.5%	4.0%

H. No Baby Data or Adequate Follow-up.
I. No Reporting of Contraception or Mother Follow-up.
J. No Social or Emotional Approach to the Mother.

Discussion

In 1922, Harris suggested age 16 as a very favorable time for a young woman to have a baby[15] because of her optimal physical condition.

Until the early 1960s the obstetrical literature[2,5,6,9,11,12,14,16,17,20,22,23,26,31,33] followed the lead of Dr. Harris and continued to view the pregnant adolescent as essentially a social problem. However, the studies reviewed did not separate the older (17 to 19 years of age) teenager from her younger (less than 16 years of age) counterpart. It was only in the early 1960s that a distinction began to be made between these groups.[10,18,21,24]

No study mentions an approach to countraceptive control and possible effects or benefits of preventing additional unwanted pregnancies or preventing a first pregnancy in the teenage girl.

The above mentioned variables become important when considering the results of the studies by Battaglia, Stein, and Zachler.[3,32,34] These studies are the latest published concerning the young teenage mother. They once again highlight the high-risk nature of the group as well as imply trends and raise questions that the obstetrician who is going to deal with the young mother will be compelled to answer in the future. Stein and Battaglia[3] cite an overall prematurity rate for females less than 16 of 18.1% while the neonatal death rate was 40.9 per 1000.[32] Efforts must be made to deal with the mortality and morbidity stemming from these pregnancies.

Prenatal Care

Zachler,[34] as well as Stein and Battaglia[3,32] demonstrate that dealing with young mothers as a high-risk group in specially designed clinics providing comprehensive prenatal care can significantly reduce the prematurity rate and perinatal mortality. In those infants born to mothers without prenatal care a significantly higher percentage died of birth injury and asphyxia, whereas in those born to mothers who had specialized prenatal care the leading causes of death were sepsis, lung problems, and other diseases peculiar to the newborn. The latter are preventable deaths.

If any type of comprehensive, long-range data concerning outcome of these pregnancies

is going to be obtained, the pediatrician as well as the obstetrician will have to involve himself early with the mother and then continue to follow both her and the baby.

Cause of Perinatal Mortality

Several investigators[1] have cited prematurity as the leading cause of perinatal mortality. The epidemological correlates in the young mother giving birth to a premature infant are as follows: Negro, poverty,[4] inadequate prenatal care, unmarried, toxemia, a previous history of prematurity and a lack of adequate child spacing.[1] Other data[8,29] has suggested that these women will go on to have a high incidence of social problems dominating their lives. The fact that most teenage mothers are unmarried also tends to place them at higher obstetrical risk as far as maternal mortality, infant mortality, premature births, and complications of pregnancy are concerned.[25]

Hennepin County Data

Turning to the Hennepin County General Hospital data, several items seem worth commenting on. That 4.4% of our total service is made up of girls under 16 indicates that a more systematic approach to these girls would not be unwarranted as far as personnel and time usage is concerned.

The fact that 26% of our mothers are married somewhat obscures the fact that 96% of these marriages took place after they became pregnant. This is a somewhat higher percentage of premarital pregnancy than other age groups.[29] However, it is also known that marriages under these circumstances don't do as well as marriages made at a later age.[7,8,29]

The Negro proportion of our series (20%) is less than that found in similar studies. However, the percentage of young Negroes seen significantly exceeds their representation in the Hennepin County population (5%) as well as the percentage of Negroes having babies out of wedlock in Minnesota (8%). These figures seem to support the conclusion of Zackler[34] regarding the increasing number of non-white young mothers to be encountered in the future. The low percentage of American Indians in our series (1.6%) raises questions concerning cultural values in relation to early intercourse and/or questions concerning where these girls deliver their babies.

Twelve and five-tenths percent of these girls receive no prenatal care at all. This seems incredible considering the fact that all girls are required by law to attend a public school. It was not possible to ascertain from our data how many of these girls continued their education either during or after their pregnancy.

The incidence of toxemia agrees well with other series. The high incidence (7.5%) of C-sections can be explained by the number of girls who deliver from the Lutheran Social Service Home, many of whom are referred specifically because of fetal-pelvic disproportion. The higher than expected incidence of prolonged labor (16.6%), premature rupture of membrances (16.6%), and postpartum hemorrhage (11.6%) is surprising and no ready explanation (other than possible differences in reporting from one institution to another) is available.

Pediatricians

Three facts should be of concern to the pediatricians working at hospitals that deal with young mothers. *The first,* and most obvious, is that by traditional standards these young mothers are themselves pediatric patients with whom little or no effective contact has been made prior to their pregnancy. *Secondly,* the high number of babies (25%) who end up being dealt with in a high-risk nursery as well as the higher than expected perinatal mortality rate (25/1000) should alert the pediatrician to the potential problems involved so that he may effectively participate in the maternal care at the earlier stage than in the past. *Finally,* most (75%) of these mothers are keeping their babies, and yet only a few of these children (25%) are receiving any type of adequate baby care. To say that they are going elsewhere for care is not enough. Any hospital that deals with the young mother has an obligation to her that transcends her delivery as well as a chance for meaningful follow-up to provide the necessary data that is needed to effectively deal with this problem in the future.

Finally, it is noted that only 44% of the total group receive an effective contraceptive device as part of their care. That the failure to provide adequate family planning leads to

ıcreased obstetrical and social risk has been emonstrated by Beasley[4] as well as others. It as been demonstrated[4] that high acceptance of amily planning methodology is possible. Furhermore, Beasley[4] has shown it possible to lecrease illegitimate births as well as repeat llegitimate births and total numbers of births n a family unit through effective family planıing programs. Whether or not one can demonstrate a reduction in perinatal mortality and norbidity in a specified group of females has ıot yet been shown and awaits further research. Parenthetically, Kinch[19] has shown that most eenage mothers have never used contraception. The question of contraception for the unmarried teenager is raised as well as possible effects of contraception on abortion rates, attitudes towards sexuality, ultimate family outcome, and overall emotional well-being of the females involved. These questions must be answered in view of the ever increasing number of young females in our population. To date, the meager data presented herein is the only reported information concerning contraceptive follow-up in a group of teenage mothers. More is clearly needed.

Summary and Conclusion

Data has been presented concerning 120 term pregnancies of girls 16 and younger occurring in 1968 through 1969 at Hennepin County General Hospital. This data demonstrates this group of females as a high-risk group that should be managed with a multidisciplinary approach. A review of the literature seems to support this view. It is urged that prospective data be collected concerning the natural history of teenage pregnancies — especially as far as ultimate outcome of both mother and baby is concerned. In addition, studies are needed to define the role of contraception in the professional approach to the teenage female.

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He that is always right is always wrong.

Laboratory Letter

Alcohol, Transaminase, and the Liver

"Elixir and Opiate; Tonic and Pain-Killer; Running Riddle and Fluid Answer; Destroyer and Preserver; Universal Solvent and Mortal Stain; Setter-On of the Dream and Taker-Away of the Performance; Joie de Vivre and LachRymus Rerum; Symbol of the Ferment in this Valley of Fog, Mist, and Tears . . ."

"Water of Life"
—Henry Morton Robinson,
Simon & Schuster, New York, 1960.

As novelist Henry Morton Robinson says, alcohol is a puzzling solution. It creates as many problems as it solves. Among the medical puzzles is this one: Does a proper diet protect the liver against alcohol? Physicians have been arguing that for at least a century, and the final returns are still not in.

Because of our experience with chemistry graphs, I am inclined to think that alcohol does cause transient, reversible liver damage, even in well-fed persons. I became aware of this when we were screening a group of executives. Many had SGOT elevations of 50 to 100 mU/ml (normal 10 to 50 mU/ml), yet few had evident heart or liver disease.

Then I happened upon a *New England Journal of Medicine* article[1]. Its authors gave subintoxicating doses of alcohol to 12 volunteers for two days, fed them a standard or a high-protein low-fat diet, and, before and after alcohol, measured their SGOTs and biopsied their livers. The mean SGOT before alcohol was 32 units and after, 43 units. Hardly an astonishing rise. But the upper limit of normal was 40 units, and half of the after-ingestion values were over 40 units. From these enzyme changes and what they observed in biopsies, the investigators concluded: "Amounts of alcohol consumed by many 'social' drinkers are enough to damage the liver, and one need never have been drunk to sustain alcohol-induced hepatic injury."

So much for convivial imbibers. Now what of the alcoholic? To get at that answer, we are currently screening with chemistry graphs a large series of alcoholics admitted to a private treatment center. Most of these patients are well-nourished, intelligent members of the middle or upper class. By clinical and chemical criteria, less than four percent have portal cirrhosis. From the 313 patients we have now screened, I have compiled this data:

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TABLE 1

Mean SGOT on day of admission when patient's last drink . . .	
Day of admission	70 mU/ml
Day before admission	55 mU/ml
3 to 7 days before	50 mU/ml
7 to 14 days before	45 mU/ml
15 to 30 days before	35 mU/ml
More than 30 days before	25 mU/ml

TABLE 2

Percent of abnormal SGOTs on dayof admission when patient's last drink . . .	
Day of admission	55%
Day before admission	31%
3 to 7 days before	27%
7 to 14 days before	26%
15 to 30 days before	13%
More than 30 days before	11%

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Hyperparathyroidism

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DAVID G. PUGH, M.D.‡

THE DIAGNOSIS of primary hyperparathyroidism is made more frequently now than a decade ago. The reasons for this increase are greater awareness of the condition and availability of more accurate methods of estimating blood calcium levels. At times, however, increased serum calcium is noted in patients who do not have hyperparathyroidism, and the hypercalcemia is due to other disease processes. The following case illustrates the difficulty in diagnosis of hyperparathyroidism.

Report of a Case

In July 1967, a 59-year-old white man with a 28-year history of schizophrenia was referred to the local state hospital for surgical correction of divergent strabismus. Results of physical examination at that time were otherwise unremarkable, and the patient was asymptomatic. A thoracic roentgenogram, made as part of the preoperative work-up, revealed an osteolytic lesion of the left eighth rib (Figure 1) associated with what appeared to be a soft tissue tumor laterally. A diagnosis of primary versus metastatic malignancy was entertained, and a comprehensive study of the patient was undertaken to locate the site of a possible primary malignancy.

Proctoscopy and barium enema studies were entirely negative, and biopsy of both lobes of the prostate failed to show any evidence of malignancy.

X-Ray Studies

The roentgenologic skeletal survey (Figure 2) showed bilateral destruction of the ischia and pubic rami, punched-out lesions of the long bones, and multiple osteolytic defects involving the ribs, skull, and mandible. These were highly suggestive of metastatic malignant disease. Differential diagnoses of hypernephroma, thyroid carcinoma, Paget's disease of the bone, and multiple myeloma were considered. However, excretory urograms and nephrotomography ruled out the presence of hypernephroma. Bence Jones protein was not present in the urine. A bone marrow biopsy did not reveal any abnormalities.

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Laboratory Studies

Laboratory data were all within normal limits except for certain values: alkaline phosphatase, 90 King-Armstrong units (normal, 14 to 35); acid phosphatase, 19.2 units/liter (normal, 7.9); uric acid, 8.6 mg/100 ml (normal, 4.3 to 8); serum calcium, 11.8 mg/100 ml (normal, 8.9 to 10.1); and serum phosphorus, 2.3 mg/100 ml (normal, 2.5 to 4.5).

The patient was referred to the surgical service for needle biopsy of the lesion noted on the thoracic roentgenogram. He remained asymptomatic with normal physical findings. Primary hyperparathyroid disease was considered at this time after review of the roentgenograms. Also serum calcium determinations confirmed the increases noted in the survey done previously.

Exploration of Neck

The chest lesion was not biopsied but a cervical exploration was done, and three parathyroid adenomas were found. Pathologic examination of the resected parathyroid and thyroid tissue revealed a tumor of the right inferior parathyroid gland, 4 by 2.5 by 1 cm and weighing 10 gm. Histologically the tumor was composed largely of chief



Fig. 1—Preoperative roentgenogram, revealing osteolytic lesion of left eighth rib associated with soft tissue tumor laterally.

cells with foci of larger *wasserhelle* cells and pale oxyphilic cells. In some areas the chief cells showed nuclear enlargement and hyperchromasia with giant cell forms but no mitotic activity. These changes were interpreted as degenerative in character. No vascular invasion was noted. The final diagnosis was parathyroid adenoma, mixed cell type, with atypical degenerative nuclear changes. Within the resected thyroid tissue, near the capsule, were two oxyphilic nodules, 0.5 and 0.6 cm in diameter. These were somewhat atypical in appearance but were interpreted as oxyphilic tumors of parathyroid origin. The remaining parathyroid gland was grossly and microscopically normal.

Postoperative Course

Postoperatively, serum calcium decreased to 6 mg/100 ml, with no indication of tetany. It has been neces sary to supplement the patient's diet with calcifero 50,000 units every other day, a 5% solution of calciu lactate, six teaspoonfuls daily, and three glasses of mil daily. The lytic lesions of the skeleton have becom sclerotic. At the most recent determination, serum calciu was 9.4 mg/100 ml and serum phosphorus, 3.4 mg/100 m

Discussion

For years, the diagnosis of hyperpara thyroidism was made only when there wa roentgenologic evidence of abnormality in th skeleton. However, with the advent of ac curate measurement of serum calcium, les

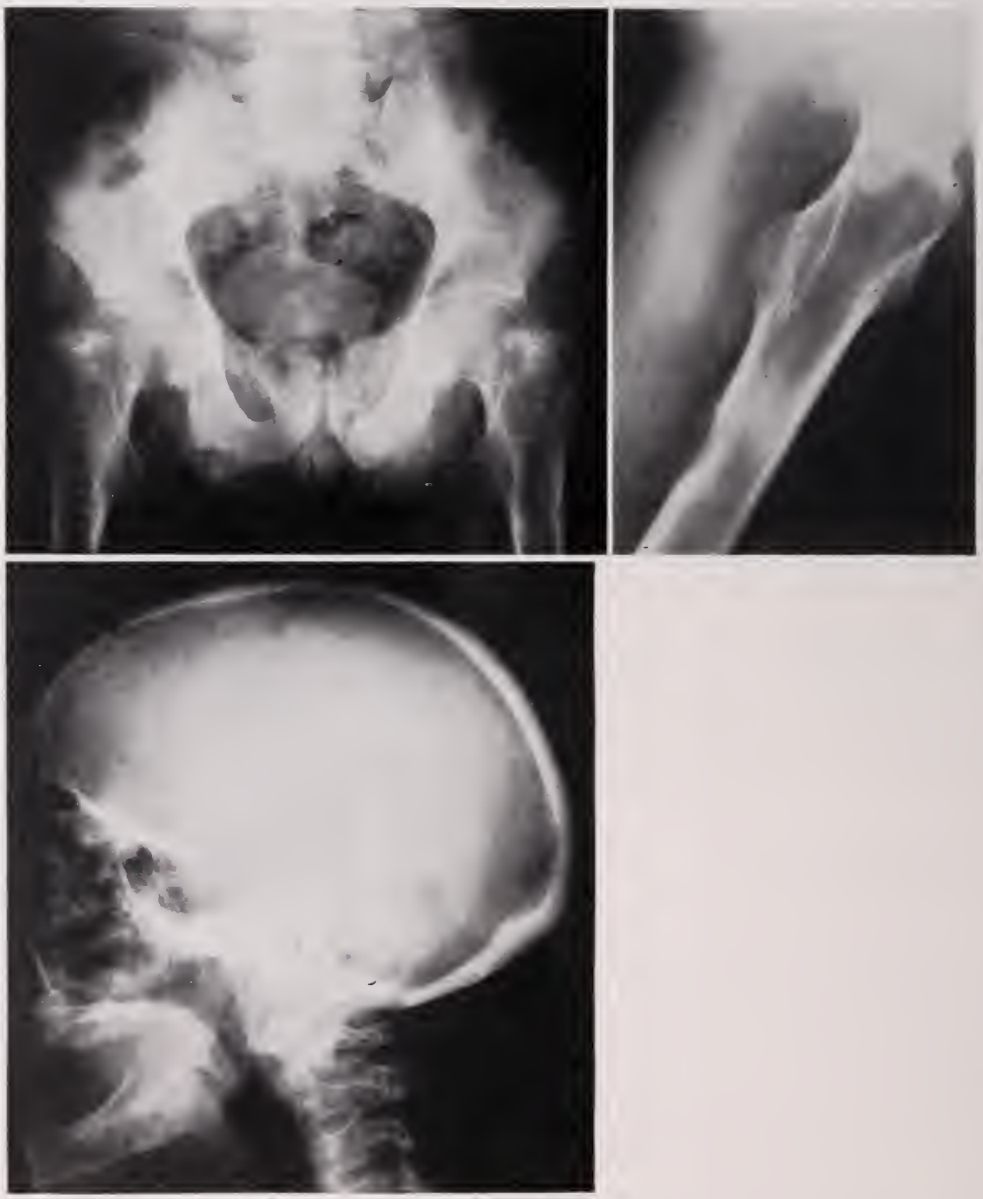


Fig. 2—Roentgenologic skeletal survey revealing bilateral destruction of ischia and pubic rami, punched-out lesions of long bones, and multiple osteolytic defects involving skull and mandible.

mphasis was placed on abnormal roentgenogic findings because these changes occur in e advanced stages of the disease. The classical cture of von Recklinghausen's disease is rely seen today.

The present patient was asymptomatic. The creased serum calcium level (11.8 mg/100 l) was consistent with the atypical bony anges suggestive of other diseases, and it was nly after much discussion and re-evaluation that the diagnosis of parathyroid disease was made.

Summary

A case of hyperparathyroidism in a 59-year-old man is presented. The findings were unusual in that the roentgenologic appearance of the skeleton suggested bony metastasis from malignant disease. After the removal of three parathyroid adenomas the bony lesions largely cleared.

School of Salernum III

The *Flegmatique* are most of no great growth,
Inclining to be rather fat and square:
Given much unto their ease, to rest and sloth,
Content in knowledge to take little share,
To put themselves to any paine most loth.
So dead their spirits, so dull their sences are:
Still either sitting, like to folke that dreame,
Or else still spitting, to avoid the flegme:
One qualitie doth yet these harmes repaire.
That for the most part Flegmatique are faire.

Editor's Note:

Lazy, squat, insensitive, fat: thus the School categorizes the flegmatic individual. Not a bad one but the sort least likely ever to startle the world with a heroic act or a revolutionary idea. Depicted as dreamily sitting and ruminatively spitting, he is easily distinguished from the other three humoral types: sublimely unresponsive and impervious to the impact of his environment; not too unlike a fat boy or Fruehlich syndrome.

Balance

At every stage the living structure concentrates on its primary task, which is to preserve itself and to follow out its allotted course. Physiology tells us that this can be successfully accomplished *only if the living organism is able to maintain the internal balance by which it holds itself together.* A counterforce—in the form of tensions, pressures and chemical changes both within and without the organism—constantly upsets this internal balance, and thereby threatens to destroy the structure as a whole. But the instinctual force of life, which works through a marvelous regulatory mechanism, opposes these destructive tendencies by restoring and maintaining the original balance.*

*Smiley Blanton, Love or Perish

Doubt

If we begin with certainties, we shall end in doubts; but if we begin with doubts, and are patient with them, we shall end in certainties.—Francis Bacon

Meet Doctor Darwin*

Horse-and-buggy doctor of Lichfield, Staffordshire, England, he could be identified from a distance by the one white horse of his team in an era when teams were customarily matched in color. Day and night he could be descried from afar, lurching and bumping over the abominable roads in his area, sometimes forced to descend from his carriage to mount a saddled horse that always walked along behind his vehicle in case impassability compelled transfer. Incidentally, like his rider this horse was called Doctor. In fact, Doctor Darwin was on the road so much that a letter was once addressed: "To Dr. Darwin—On the Road."

That his phenomenal success and unorthodox methods made him unpopular with his more conventional colleagues disturbed him not a whit. He went anywhere any time to anyone who needed him.

When he arrived he expected a substantial meal to be awaiting him, to be consumed leisurely before he stepped into the patient's room. For, said he, appetizing viands reinvigorated him after a harrowing ride, making him brighter and brisker and hence more acceptable to the patient.

Few patients ever knew what to expect. As Darwin maintained that many ailments were only imaginary or at most functional, he devised exotic treatments calculated to induce surprise, wonder, apprehension, possibly even terror, in order to jolt the patient back to normality and sanity, where he usually remained, not caring to undergo a repetition of the initial assault.

Besides shocking his patients emotionally, he employed more literal shock in the form of electrical currents passed through crucial areas. "Mr. Seville had laboured several weeks with the jaundice, and taken calomel, steel, oil, etc., in vain—he had no pain, nor sickness, nor fever. I had pretty potent electric shocks passed through the body and taken out about the region of the gall bladder, and he began to mend the next day, and on continuing the electricity recovered fast."

Definitely ahead of his time he believed that free discussion between physician and patient was beneficial, a practice seminally suggestive of modern psychoanalysis.

Darwin's biographer, Hesketh Pearson, calls him an all-around man. He was interested in everything and, while on his perpetual calls, his body tossing and careening over boulders, ruts, and ditches, his eclectically-oriented mind was free to tangent off in any direction: observing, pondering, deducing. He even wrote monographs while riding, a feat attesting to his constitutional toughness. Phonetics, pollution, Plato, phosphorus, ploughs, plants: all engaged him.

Endowed with prophetic intuition as an adjunct to keen intelligence, Darwin glimpsed, albeit prematurely and only rudimentarily, the theory of Evolution, the biological principle his grandson Charles was later to develop and establish. Truly an all-around man as well as a doctor!

---

*Erasmus Darwin (1731-1802), grandfather of Charles Darwin.

With acknowledgements to and quotations from Hesketh Pearson: Doctor Darwin, 1930, and Extraordinary People, 1965.

Progress always involves risks. You can't steal second base and keep one foot on first.—Future



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In his daily practice the physician witnesses the human suffering caused by uncontrolled fertility. Perhaps one of its most tragic effects is the unwanted child, who so often experiences parental rejection. The rejected child in a family may be neglected, nagged and severely punished. Sometimes he is criminally abused. Child abuse is common enough to have become a separate clinical entity: the "battered child" syndrome. Reliable statistics are difficult to obtain, but it has been estimated that in this country alone roughly 10,000 children are "battered" per year, and their number may be increasing.

A revealing picture of child abuse patterns is provided by one study of the American Humane Society. More than half of the 662 children involved (all reported in newspapers within a single year) were less than 4 years of age. One fourth of the battered youngsters died; most of these deaths wer of children less than 2 years of age. Fathers were more often guilty of child abuse than mothers, but sometimes both parents participated. The study indicated that battered children are not limited to any particular socioeconomic stratum.

***For the complete brochure, and others in the seri as they appear, please write to Searle or ask your Searle representative.** Explored in the forthcomin issues will be the history of birth control, the influen of poverty, ethnic factors and marital status, its role in illness, its genetic implications and its effects on the emotional and behavioral life of the individual.

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Special note—Oral contraceptives have been marketed in the United States ce 1960. Reported pregnancy rates vary from product to product. The effec- eness of the sequential products appears to be somewhat lower than that of e combination products. Both types provide almost completely effective con- ception.

An increased risk of thromboembolic disease associated with the use of hor- nal contraceptives has now been shown in studies conducted in both Great itain and the United States. Other risks, such as those of elevated blood essure, liver disease and reduced tolerance to carbohydrates, have not been antitated with precision.

Long-term administration of both natural and synthetic estrogens in subpri- ate animal species in multiples of the human dose increases the frequency of me animal carcinomas. These data cannot be transposed directly to man. he possible carcinogenicity due to the estrogens can be neither affirmed nor futed at this time. Close clinical surveillance of all women taking oral contra- eptives must be continued.

Indication—Ovulen and Demulen are indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disor- ers, cerebral apoplexy or a past history of these conditions, markedly impaired ver function, known or suspected carcinoma of the breast, known or suspected strogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of hrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary mbolism and retinal thrombosis). Should any of these occur or be suspected he drug should be discontinued immediately.

Retrospective studies of morbidity and mortality conducted in Great Britain and tudies of morbidity in the United States have shown a statistically significant ssociation between thrombophlebitis, pulmonary embolism, and cere- ral thrombosis and embolism and the use of oral contraceptives. There have en three principal studies in Britain[1-3] leading to this conclusion, and one[4] in his country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4 4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thrombo- embolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Ovulen and Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Ovulen or Demulen. Therefore, if such tests are abnormal in a patient taking Ovulen or Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen or Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen or Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen or Demulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen or Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

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Editorials

Screening for Stroke-Prone Patients*

Dr. Capistrant and Dr. Gumnit have described an interesting modification of the use of thermography for detection of altered perfusion from the internal carotid artery (Minnesota Medicine, May, 1971). There seems little doubt that this modification, using a head clamp to occlude both superficial temporal arteries, enhances the contrast on the thermograph of abnormal subjects and thus increases the frequency of detection of altered flow in the appropriate internal carotid artery.

In the last 15 years or more, a number of procedures have been devised or commonly used to detect altered flow in the internal carotid artery. In addition to the thermographic technique, these include retinal artery pressures as measured with an ophthalmodynamometer, fluorescein circulation time to the retina, orbital plethysmography, an ultrasound device using the Doppler effect, and a simple thermistor thermometer to measure temperature in the medial supraorbital region. Some investigators have suggested that simple temperature measurement with an inexpensive thermistor is almost as effective as the thermograph which costs about $30,000.

The most that any of these techniques can offer is evidence that flow or pressure in one internal carotid artery is reduced. Even assuming high accuracy, detection of such an abnormality does not allow us to presume high risk of an ischemic stroke in an asymptomatic individual. We have known for some time that of an autopsy population more than 50 years of age at least 30% have had severe stenosis or occlusion of one or more arteries in the cervical region although no cerebral ischemic symptoms were present during life.

Although detection of altered flow in one internal carotid artery is pertinent in evaluating patients with cerebral ischemic symptoms, experience at this point has led most investigators to believe that transient focal neurologic symptoms (TIA or transient ischemic attacks), which may occur repeatedly prior to a stroke, are not often caused by poor distal perfusion from reduced flow in a large proximal artery. Instead, in most cases these attacks appear to be caused by microemboli arising from an ulcerated atherosclerotic plaque. The plaque may be associated with moderate or even severe arterial stenosis, but occasionally such microemboli seem to stem from an ulcerated plaque that does not compromise the flow in the involved artery. Evidence of microemboli occasionally is detected with ophthalmoscopy of one or more bright cholesterol crystals in the retinal arterioles.

Transient ischemic attacks seem to represent a serious risk for development of stroke. In some age groups the risk for persons with transient ischemic attacks may be 10 times higher than in other persons in the same age group. Transient ischemic attacks and hypertension probably represent the most important risk factors for stroke that can be altered potentially by the physician.

At this time it is difficult to make a case for screening the stroke-prone individuals among asymptomatic persons by means of an expensive clinical tool. The most important screening techniques are a carefully obtained history from the patient and a recording of the brachial blood pressure in both arms. Further clinical investigation in regard to effective techniques for detecting stroke-prone individuals is a continuing need.

Jack P. Whisnant, M.D.
Rochester, Minnesota

*See page 689.



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Computer-Aided Medical Decision Making*

A DIGITAL COMPUTER has the capacity to store information and perform a large variety of predesignated arithmetic and logical instructions. This capacity should intrigue the physician. These capabilities theoretically offer him an entirely new and powerful source of aid in the complex decision-making which he faces daily.

At least four types of problems must be solved, however, before computer-aided medical decision-making becomes a reality. These problems are related to (1) designation of areas of application, (2) technical methods, (3) costs, and (4) evaluation.

The physician should take an active role in the designation of areas of application. He is in an excellent position to recommend fruitful projects. It should be emphasized that this task requires both insight into the problems of medical practice and a degree of creativity and originality. For example, certain decisions such as anatomic and histopathologic diagnoses might appear to be the obvious first choices for study. However, are anatomic diagnoses always the best concepts of application or should more fundamental medical decisions and actions be studied? These determinations might include decisions to order additional tests, to request special consultations, to transfuse, to request a biopsy, to operate, to treat with a specific drug, to order a special diet, or to dismiss from the hospital. These latter decisions are, in fact, implications of the so-called diagnoses but are of much greater importance to the patient. A study of actions would tend to focus attention on the dynamic physiologic status of the patient rather than to dwell on the often purely academic histopathologic classifications of disease processes.[1]

The second problem relates to technical, logical, and programming problems. Given a set of data and a group of possible decisions that are dependent on the data, a rule of procedure or algorithm must be used to "map" the data into the "best possible" decision. The method most easily formulated by physicians may be the formalization of the branching logic commonly used by the practicing clinician. While laborious, this method has the advantage of having great flexibility and of being rooted in the physician's prior knowledge and experience. On the other hand, subsequent modifications of the original algorithm on the basis of new information may necessitate a complete revision of the decision tree. This type of logic has been used successfully in the analysis of the electrocardiogram.[2]

Alternately, many methods are based on more sophisticated mathematical concepts.[3-9] Such methods include Bayes' theorem,[4,8,9] discriminant functions,[4,7] utility functions,[5,6,9] information models,[3] and various types of "linear and nonlinear machines".[7] A disadvantage of such models is that usually underlying each is at least one assumption concerning the independence of the variables, the form of the distributions of the variables, or the validity of the addition or multiplication of certain quantities. When applied to practical situations, these assumptions are not always realistic. If such assumptions can be accepted, however, the mathematical methods are usually considered to be superior in their utilization of the available information and in their capacity to utilize the computational advantages of the computer. This is so because with most of these methods all the variables are considered more or less simultaneously and commonly incorporate mathematically rigorous optimization principles in their derivations. A discussion and an example of the application of Bayes' theorem are published in the February issue of MINNESOTA MEDICINE.[10]

The next great problem is cost.[11] Costs are currently reflected in the difficulties physicians experience with access to the computer and in the time it takes for the physician to receive the computer output. Low-cost storage and communication devices are greatly needed so that access and turn-around time do not inhibit the practical introduction of computer technology into medicine.

The final and possibly the most perplexing problem is that of evaluation. Regardless of episodic fanfares, it is perfectly obvious that in order to be generally accepted, the computer-aided physician must function significantly better than

*Bégon, F., and Dhumeaux, D.: The Application of Computer Techniques to the Laboratory: Diagnosis of Diseases of the Liver and Biliary System. Minnesota Med 54:101, 1971.

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Indications: Serious infections due to susceptible strains of *E. coli*, Proteus sp., *Enterobacter aerogenes*, *K. pneumoniae*, *Serratia marcescens* and *Mima-Herellea*. Culture and sensitivity studies should be performed.

Contraindications: A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other agents may be a contraindication if effective alternative therapy is available.

Precautions: Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantre[illegible] nitus or hearing loss occurs. Hydrate patients to prevent chemical irrita[illegible] the renal tubules. Assess renal function periodically, both before and [illegible] therapy. If signs of renal irritation occur (casts, cells, proteinuria) increase d[illegible] tion and reduce the dosage or the frequency of dosage if necessary – in az[illegible] patients the frequency (in hours) of doses may be obtained by multiply[illegible] serum creatinine by 9. If azotemia or oliguria occur, discontinue thera[illegible] M[illegible] cotic or bacterial superinfection may occur.

Adverse Reactions: Irritation or pain at the injection site, skin rash, dru[illegible] ev[illegible] headache and paresthesias.

Dosage and Administration: The maximum total daily dose should not [illegible] ee[illegible] 15 Gm. by all routes of administration. The usual dose is 7.5 mg./Kg./[illegible] ou[illegible] I.M. The average adult dose is 1 Gm. daily. Uncomplicated infections e[illegible] sensitive organisms should respond in 24 to 48 hours.

If no response occurs in 3 to 5 days, stop therapy and recheck the b[illegible] er[illegible] sensitivities. Hydrate patients well to minimize renal irritation. Inject dee[illegible] in[illegible] the upper outer quadrant of the gluteal muscle. Discard partially used vi[illegible] ate[illegible] 48 hours. The drug should not be physically mixed with other antimicr[illegible] a[illegible]

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ıe physician alone, and the advantage of this lliance must be worth the costs of dollars, time, nd effort. The transformation of an ingenious echnical demonstration into a practical and gener- lly accepted procedure has never been an easy ısk. It demands the dedication of both phy- icians and computer specialists to develop evalua- ion techniques that will unequivocally demon- trate the true value of the new methodology. In he long run, no number of testimonials regarding he efficaciousness of computer-aided decision- naking in either medical education or medical ɔractice will suffice. New imaginative and ob- ective modes of evaluation and justification must ɔe developed.

The foregoing discussion suggests a series of questions that will enable any physician to assess a computer application for himself: "Is the computer application appropriate?" "Are the proper data being utilized?" "What are the underlying assumptions of the methods?" "Are these assumptions valid?" "What are the costs?" "What are the documented benefits?" "Do the benefits justify the costs of dollars, time, and effort?" When the answers to all of these questions are favorable, we will have bridged the jargon-gap and will be directed toward the true goal of more effective delivery of medical care.

Despite all difficulties, the potentials of the digital computer are so great that even the most critical reader would probably admit to the likelihood that eventually computer-aided medical decision-making will in some manner become an integral part of medical practice. Preparations for such an event, therefore, become the responsibility of all of us. Of primary importance is the willingness of the physician to entertain the possibility of innovation and to accept eagerly new concepts of proved value. For those individuals whose interests are even more intense, it is important to participate in professional organizations that present professional advancement programs in biomedical computing in a context and a level of complexity that is appropriate for the physician. One such organization is SIGBIO: the Special Interest Group in Biomedical Computing of the Association of Computing Machinery. Membership is open to all individuals who are interested in biomedical computing. Physicians are cordially invited to join in the activities of this organization. Finally, as responsible physicians, we should all welcome, as important colleagues of the allied health professions, the well-trained computer specialists who can provide the technical skills necessary for complete exploitation of the computer in medicine.

Robert C. Bahn, M.D.*
Rochester, Minnesota

*Consultant in Section of Experimental and Anatomic Pathology, Mayo Clinic, and Professor of Pathology in the Mayo Graduate School of Medicine (University of Minnesota); chairman of the Mayo Computer Committee; Membership Chairman of SIGBIO. Inquiries concerning SIGBIO may be addressed to Dr. Bahn in care of the Mayo Clinic, Rochester, Minnesota.

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Breathing Exercises for Obstructive Pulmonary Disease

Breathing exercises have been prescribed for many years for diffuse obstructive airway disease—specifically chronic bronchitis and emphysema. This therapeutic modality continues to be commonly used despite many studies that have failed to demonstrate any physiologic benefit.[1-4] Barach[5] and Miller[6] have reported more encouraging quantitative findings in various studies involving large numbers of patients.

The diaphragm is usually low in chronic obstructive pulmonary disease and the residual volume is greatly enlarged. Thus, therapeutic emphasis is concentrated on expiration (usually passive in normal subjects) involving use of the abdominal muscles. The patients have been found to have respiratory muscles of at least normal strength,[7] and cough pressures are high or normal. Diffuse airway obstruction and not muscle weakness appears to account for the reduced maximal airflow and breathlessness in patients with bronchitis and emphysema. Mead and co-workers[8] demonstrated that the high airflow resistance in emphysematous subjects is further accentuated by increased expiratory effort, which apparently results from the collapse of poorly supported airways. The key to the subjective benefit of breathing exercises, therefore, seems to rest in slow, even, moderately forced expiration.

Pursed-lip breathing (exhalation) in emphysematous subjects has been considered to have significant effect in decreasing the respiratory rate, increasing the tidal volume, possibly increasing ventilation in poorly ventilated portions of the lungs, and decreasing the arterial carbon dioxide tension, which may be elevated in advanced cases. The value of pursed-lip breathing is more likely related to a slower initial expiratory flow rate. Schmidt and associates[9] demonstrated larger vital capacities in emphysematous subjects with an initial slow expiratory effort than in those with maximal effort, which seems to accentuate the check-value effect.

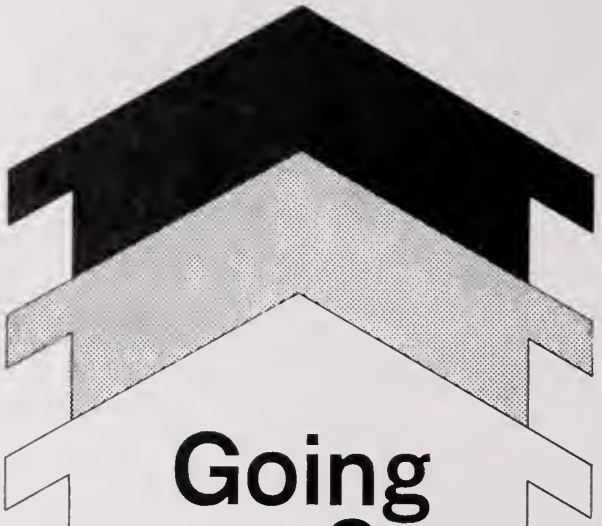
In light of the increasing volume of quantitative information, breathing exercises should promote slow, smooth abdominal or "diaphragmatic" respiration with protrusion of the abdomen as the diaphragm descends on inspiration and flattening of the abdomen on expiration with contraction of the abdominal muscles in a gentle but steady and prolonged action. Since this is not a normal breathing pattern, it must be practiced and renewed under supervision much the same as is done by an operatic singer. It is difficult but not impossible for patients to practice abdominal breathing while walking. Some patients find it easier to concentrate on abdominal muscle function while standing still, relieving dyspnea more promptly than with untrained, more thoracic-oriented breathing. Initially patients must learn abdominal breathing while recumbent and relaxed, as mentioned recently in this journal.

Abdominal breathing appears to be essential for increased elimination of carbon dioxide since this is not accomplished by deeper thoracic breathing by emphysematous patients or to the same degree even in normal subjects.

Breathing training is likely to be effective when incorporated into a well-rounded program including avoidance of respiratory irritants (especially smoke), regular use of aerosol or oral bronchodilators or both, adequate hydration, walking exercise to improve the general health (sometimes with low-flow oxygen inhalation when indicated), and the prompt use of medically prescribed antibiotics for respiratory infections. While no one of these modalities brings spectacular results consistently, a coordinated program initiated with detailed, reinforced instructions may help a significant number of patients with this usually progressive disease. The concept of a special clinic enhances the delivery of multifaceted therapy by a health-care team to an increasing number of respiratory patients.[10]

R. Drew Miller, M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation: Division of Thoracic Diseases and Internal Medicine.
References may be secured from the author or the reprints.



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Homage to the Class of 1921*

EACH YEAR at its annual May meeting it is the pleasant custom of the State Association to honor those hardy physicians who have practiced a half century in the State and are inducted into the Fifty Year Club. This year there are 27. Short biographies of each will be found elsewhere in this issue of MINNESOTA MEDICINE. Six are distinguished alumni of the Mayo Clinic Faculty. Others include prominent men in many fields: obstetrics, general practice, surgery, and internal medicine. They have all contributed their life work to Minnesota and deserve the thanks not only of the medical society but of all the citizens whom they have benefited.

Some of them will recall the following vignettes culled from Volume 3 and 4 of MINNESOTA MEDICINE printed fifty years ago under the editorship of Dr. Carl Drake.

Minnesota Academy of Medicine, November, 1919.

Case report of Dr. R. E. Farr: A nine-year-old boy was struck by the fender of an automobile. He was dazed but able to walk. Two hours later he was seen by a physician, and the injury pronounced not serious. Six hours later he grew suddenly pale, and when Dr. Farr saw him the pulse was gone and he was gasping for air. He was given 300 cc of blood at once without stopping to test the donor. Meanwhile the abdomen was opened under novocaine. Much blood was found from a ruptured liver. The wound was packed, and the abdomen rapidly closed. Two assistants and the donor remained at the hospital and were called upon to transfuse 300 cc more blood during the night. Seven days later (at the time of this report) the boy was doing well. *(The method of transfusion probably was withdrawal of whole blood and immediate infusion into the patient. ABO typing was the rule, and this an heroic exception.—Editor)*

The Function of Minnesota Medicine:

MINNESOTA MEDICINE is starting its third year. Its excuse for being is mainly to make available to the profession the experience and knowledge of medical men located for the most part in Minnesota (unsigned editorial).

Epidemic Influenza

A report of 296 cases seen at the University of Minnesota Hospital in one month in the fall of 1918: The death rate was 22.6% overall and for the pneumonias, 54%. Therapy . . . Phlebotomy with infusion of Fischer's solution. This was employed in 23 cases to relieve toxicity and circulatory embarrassment. Twenty-one had a fatal issue. (Edgar T. Hermann).

Of General Interest

The federal income tax for the year 1919 is due March 20, 1920. The so-called normal tax is 4% on the first $4000 and 8% above $4000.

Acute Dilatation of the Stomach

At Bethesda Hospital we have been using a device consisting of a three-way stop-cock connected to tubes in such a manner that water is first syphoned into the stomach from a pail held a couple of feet above the level of the patient, and then by a change of the connection syphoned out of the stomach through a tube leading to a pail on the floor. (O. W. Holcomb).

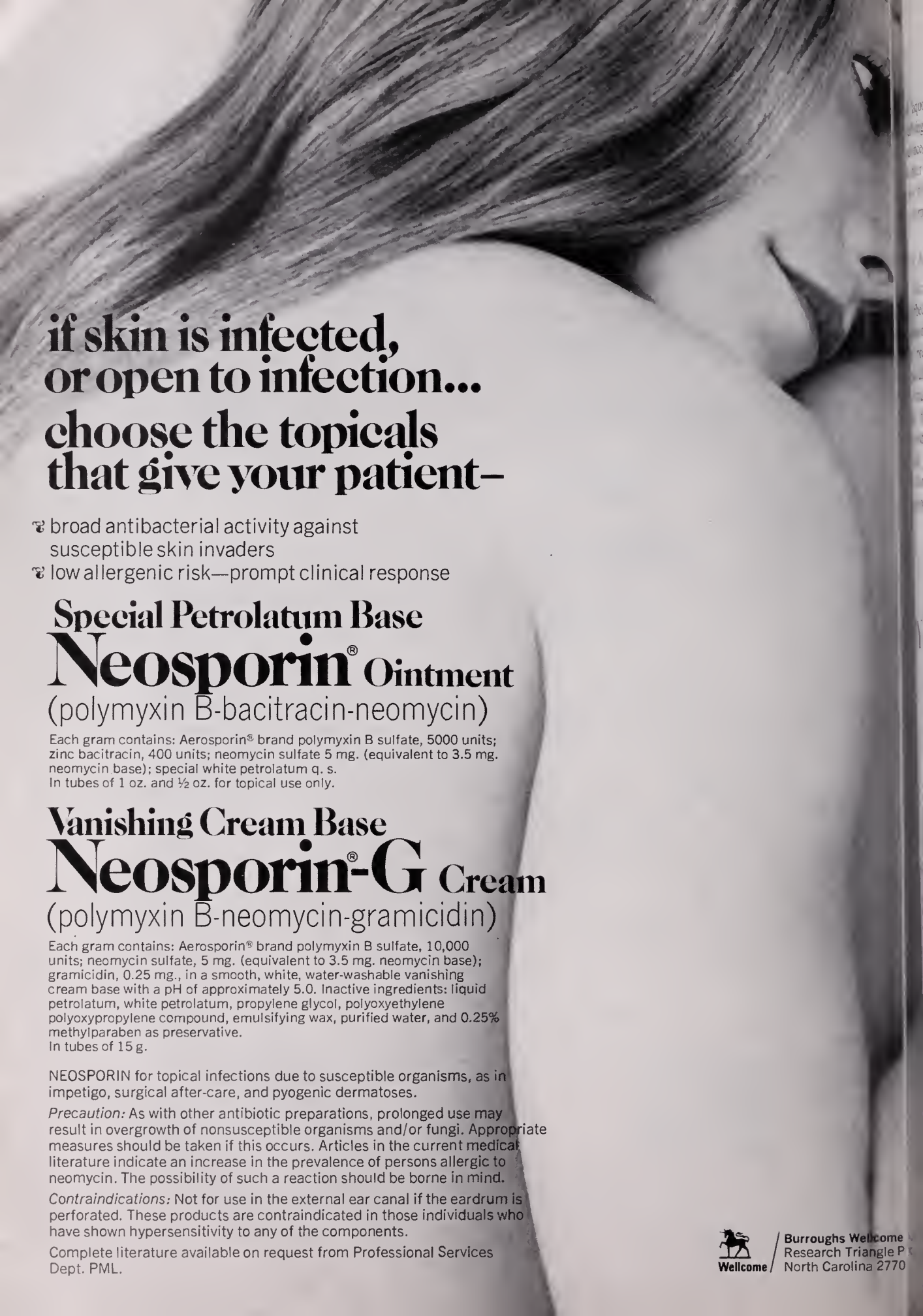
A Study of Diabetic Patients With Surgical Complications

One hundred and fifty-nine operations of all kinds have been performed in the (Mayo) Clinic on diabetic patients with a mortality of 5.03%. (D. M. Berkman).

Compulsory Health Insurance and the Medical Profession

It is by deliberate conclusion that the social and economic status of the lower classes of physicians has been appreciatively raised, but that at the same time the standard of the higher class has unquestionably been lowered. Entirely too much time and thought is wasted on deliberations which concern questions of remuneration and conditions of medical practice. (F. L. Hoffman of the Prudential Life Insurance Co.)

*See page 733.



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of liquor. For the most part promiscuous prescribing has been done by those with elastic consciences or none at all for the fee attached. Rather strong pressure is exerted at times when your friend wants a nip, and you are in a position to furnish it.

The Acquisition of Useless Knowledge

The premedical and medical course as prescribed in Class A medical schools under the stimulation of the American Medical Association is at present so thoroughly filled with ostensibly useful subjects, each of which is allotted exactly so many departmental hours, that there is no time left for useless subjects. The medical student spends the first third of his life in learning, and a little more than the second third in the service of humanity. The weak point in our present time apportionment lies in the fact that after two-thirds are gone, there still remains another third at the end of life for which frequently no preparation has been made. Thus the man who knows only the science and art of his own profession and ostensibly entirely abandons interest in both when he retires from practice is a sadly misplaced unit in the community. He is apt to commit agriculture, California, or suicide. Indeed the retired professional man who has no hobby, no perfectly useless bit of knowledge with which he may play, is apparently a fit subject for euthanasia. (Louis B. Wilson. President before the Medical Six O'Clock club May 24, 1921.)

Times change but the problems don't. The Medical Six O'clock Club was a great institution and should be revived. There is still need of useless information in our tower of medical learning.

Reuben Berman, M.D.
Minneapolis, Minnesota

You May Be Right

A Thought Re Augmentation Mammoplasty

A man, holding a grease gun with a pressure of 60 pounds, accidentally triggered the pointed nozzle into the palmar surface of the distal phalanx of his mid-finger. This immediately produced a distended, tense, sensitive mass. Scarcely any point of entry was observed. A stab wound incision failed to release any appreciable amount of grease. A second stab wound a few weeks later likewise released no grease.

Gradually the mass softened. No necrosis or infection developed. The initial tenseness and sensitivity disappeared in three weeks. Now, one year later, is it causing no symptoms. The finger has been left with a large, soft, padded-appearing volar surface throughout its distal phalanx. The depth of this small area of distal phalanx is approximately twice normal. X-ray revealed uniformly distributed pinpoint particles.

Perhaps the injection of non-absorbable fat, grease, plastic, through a small needle with multiple microscopic holes directed toward the breast substance, in the areolar area between the breast tissue and the pectoral muscle, injected under rapid, controlled "grease-gun pressure" might give the same permanent enlargement in an underdeveloped breast.

Experimental studies on animals should readily demonstrate the accuracy, the feasibility, and the possibility of applying this method to augmentation mammoplasty.

The individual with the accidentally injected finger has a completely painless, smooth, soft, normally sensitive distal phalanx. No reconstructive surgery is contemplated.

Carl O. Rice, M.D.

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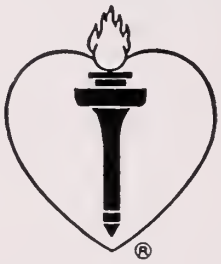
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Editor's Soliloquy

Biological Perils

When Pascal commented on man's potential for both lofty intellectual achievement and base moral depravity* he might appropriately have scored human folly as well: man's penchant for disregarding and even defying the inexorable laws that ensure optimum physical, mental and social integrity and capability. Man abuses his body, mind and soul, and then deplores its reprisal.

Life can be tough!

The twin watchwords for the avoidance of such retaliation are unremitting *will-power* and relentless *self-discipline.* The roster of penalties is manifold and insidious, running the gamut from minor to major: musculoskeletal atrophy from sedentariness; spinal curvature from faulty posture; cirrhosis of the liver and mental deterioration from intemperate imbibing; obesity and a dowager's hump from overeating; biliary dyskinesia and a depraved mind from excessive "cantankerousness;" peripheral-vascular-pulmonary disease from smoking-tobacco; hypertension from obesity, emotional crises from profitless worry; cardiac arrest or consciencitis from too many close calls.

Is it worth it?

And that's not all! There are other nemeses: eye strain and failing vision from flickering TV screens; nerve deafness from loud combo bands; chronic nasopharyngeal inflammation from habitual nasal sprays; severe burn and incipient cancer from too avid sunbathing; venereal disease from social decadence; drug reliance from unnecessary and prolonged medication; gene mutation from LSD; loss of ambition and incentive from over-generous Social Security and Welfare allotments; and finally, senility and deficient cerebration from a combination of these.

Do you think we can make it?

To sum it all up: we can't cheat on our biological endowment without retribution. The proverbial mills of the gods never cease grinding.

—Carl O. Rice, M.D.

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*Man is the glory and the scum of the universe.—Blaise Pascal.

OLD DOC HESS SAYS: The creation of an unnecessary wall of secrecy leaves the intended beneficiary vulnerable to every vicious rumor.

I restrict myself within bounds in saying, that, so far as I have observed in this life, ten men have failed from defect in morals where one has failed from defect in intellect.—Horace Mann.

Painter Physicians

We are looking for paintings by our reader-physicians to put on the covers of MINNESOTA MEDICINE. If you have a painting to submit, please write Dr. Carl Rice, 1224 Metropolitan Medical Building, Minneapolis 55405.

(Continued from Page 681.)
for providing *comprehensive* and *continuing* medical care for his patients. Further, a definition of family practice is the application of the principles and techniques of family medicine for the provision of continuous and comprehensive health care of the patient.

There is no question or controversy at this time, as there was decades ago, concerning the importance of the primary physician in the health care spectrum, and the necessity for his perpetuation and training. We are now able to concern ourselves with the academic discipline of family practice, a body of knowledge which can be taught, is indeed being considered a distinct entity, and is being treated as such in our medical educational institutions.

Third, we have favorably affected the archaic methods of medical education; we have forced our medical educators to recognize that the function of medical schools is to produce the best possible physician and not, as formerly, to serve only to select and graduate medical students. It should be emphasized that through our efforts, particularly here in Minnesota, lay people have become our spokesmen and, to that end, states have passed legislation demanding that departments of family practice be developed in their medical schools. Our medical community should be aware of the fact that approximately 38 medical schools have in operation, or in early stages of development, departments of family practice to train future family physicians.

Last, and most important, despite the blasting headlines of successes in organ transplant, we have increased the ranks by hundreds of those students who believe in the concept of treating our patients not as horizontal disease entities but as vertical human beings. Indeed, we have discovered that there still remains in medicine a strong humanitarian ethic with which these students can identify.

As physicians we should ask ourselves why and how the idea that the general practitioner, the LMD, was somewhat less of a doctor than his specialist colleague? Research on this question reveals that at the time of World War II we learned a lot about saving lives as well as about killing. The "explosion" of medical knowledge begun at this time reached staggering proportions in the 1950s and 1960s. Indeed, it was calculated that more had been learned about disease and how to cure it in the last quarter century than in all recorded history: an awesome fact for a young man or woman, who would cure illnesses, to contemplate.

So it became fashionable to make such statements as "medicine is so complex today that no one can hope to know all there is to know about it," the implication here being that no one would dare to practice general medicine. This kind of thinking, along with some help from the Armed Forces (which supported specialty residencies during the war), virtually assured the rise of limited medical specialties. This was fine, but at the same time not so fine, as it tended to devalue the primary-care doctor who treated the whole patient and the patient as a whole.

Virtually all the federal funds that fueled the "knowledge explosion" went into research. Who did the research? Specialists. Who attracted grant money to medical schools? The specialists who did the research.

The irony of the situation was that at the time when more and more doctors were flocking to the specialties the public demand for comprehensive health care was rising to unprecedented heights. The upshot has been that medicine, the humane profession, has become or seemed to become increasingly dehumanized and institutionalized—in the face of the greatest demand ever for its healing balm. This dehumanization more than anything else has implemented the politically expedient, largely unjustified charge, that medicine is a disinterested monopoly preying on the suffering of the masses.

What is a Diplomate of the American Board of Family Physicians? During the past 18 months, the newest of the specialty groups has arisen on the medical horizon. His qualifications have been thoughtfully considered by important commissions and by committees within and without organized medicine; and, after lengthy discussions by knowledgeable clinicians and medical educators, organizations charged with the responsibility of making such decisions have created and approved essentials for graduate training in family practice. The American Board of Family Practice has given official recognition to this area of primary care as a specialty. Examinations have been given to approximately 5,000 acceptable candidates, and presently 3,500 diplomates have passed the intensive two-day certifying evaluation. Their col-

(Continued to Page 740.)

Keratoacanthoma

KERATOACANTHOMA is a rapidly evolving, non-metastasizing lesion which heals spontaneously. Unfortunately, clinically and histologically it bears a close resemblance to squamous cell carcinoma, and herein lies the difficulty associated with this lesion. The differentiation is critical.

Keratoacanthoma was described as an entity in 1950, and since that time numerous papers have appeared concerning its nature. This tumor may present itself as a solitary lesion or, in rare instances, as multiple, recurring tumors. The former or solitary keratoacanthoma is the more common condition. It occurs in older individuals, usually on the exposed areas (dorsal hands and face), beginning as an invagination of the epidermis containing keratin. As growth continues, the edges of the epidermis surrounding the crater become elevated as the keratin crater expands. Current opinion holds that these tumors result from a reactive hyperplasia of the infundibulum in the hair follicle. The tumor grows rapidly, reaching its maximum size within one to two months. The exceptions are those lesions which develop at the mucocutaneous junction of the lip. These have a tendency to enlarge over a longer period of time and to reach a greater size prior to involution. Normally the tumor, when fully developed, is 1 to 2 centimeters in diameter and dome-shaped as a result of the central crater filled with keratin. The tumor then slowly involutes over a period of five to 12 months. In most instances a slightly depressed scar remains. Early in its growth this crater usually



Figure

is not prominent, resulting in a close resemblance to squamous cell carcinoma.

Histologic examination must be relied upon for differentiation from a neoplastic growth. It is important to excise adequate tissue for examination. The specimen should include the center and both margins of the tumor. Keratoacanthomas microscopically reflect a high degree of keratinization which is found in the individual cells as well as in the keratin-filled crater. Another characteristic is the epidermal "lip" at the periphery of the crater, but this is not always present. The keratinized epidermal cells show irregular proliferations into the dermis at the base of the crater. However, all cells reflect a considerable degree of keratinization and no frank invasion by individual anaplastic cells is seen.

Multiple keratoacanthomas are a rare hereditary condition. The lesions closely resemble the solitary form of the disease both clinically and histologically. In this disorder the tumors may appear at an earlier age and continue to occur over the life of the individual. All stages of development may be seen in the same individual. Healing is with scar formation.

Treatment of a lesion suspected of being a keratoacanthoma consists of excision and histologic examination. If the histologic examination confirms the diagnosis, then simple excision as performed for the biopsy is adequate. However, if any doubt exists, then management should proceed on the same basis as for squamous cell carcinoma.

Willard C. Peterson Jr. M.D.
Minneapolis, Minnesota

FASTING FOR OBESITY

Intermittent fasts—five to 14 days—in the correction and control of intractable obesity afforded the opportunity for clinical evaluation while the patients lost 0.7 to 1.8 kg per day. A subjective sense of well-being and lack of hunger was attributed to the hyperketonemia provoked by the fast. Pregnancy, uncontrolled labile diabetes, peptic ulcer, and recent hepatic and myocardial disease were considered contraindications to the total fast. During the fast, water, noncaloric beverages, weak tea, and coffee were allowed. Serum electrolytes, cholesterol, CO_2, fibrinolytic activity, and steroid excretion were normal, although the urinary loss of NaCl exceeded the normal initially. Previously undiagnosed hypertension, diabetes, prediabetes, and cholelithiasis were frequent findings. Fasting reduced all cases of mildly elevated blood pressure to normal. Diets of 1,500 to 2,300 calories daily, with one- or two-day fasts at seven to 10-day intervals, served to reduce the weight further while permitting a more liberal diet on a day-to-day basis.

Courtesy of References and Reviews
Journal of the American Medical Association

Duncan G., Jenson, W., Cristofori, F., and Schless, G.: Amer J Med Sci 245-515, 1963.

Joys of the Table

No one can orient cooking as the physician can. He knows that taste and smell are functionally a unit. He knows therefore that it is better to replace the floral centerpiece—which finally makes the flowers smell of food and the food taste of flowers—by fruits, whose aroma does not interfere with that of food.*

*Felix Marti-Ibanez, M.D.: The Pageant of Medicine, 1960.

The unconscious direction of our lives is often more important than the conscious intention.—Oskaloosa (Iowa) Tribune-Press.

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Fifty Years of Faithful Service

J. J. Ahlfs, M.D.

Of all my time in years of practice—in Northwestern Minnesota, North Dakota, South Dakota and Eastern Minnesota—I remember the early years the best. I recall my first patient was a 17-year-old girl with a ruptured appendix. I operated, removed the appendix, inserted a drain, and she did fine. And I recall my wife—an ex-teacher—giving ether drop anesthesia, as I operated on patients lying on the kitchen table.

And I remember humorous things, too. I will mention two.

I was called one day to see a man with back pain. I did not know him well, but knew he was very religious. He apparently was suffering from kidney stone colic. It was between spells when I saw him. I questioned him just how and where it hurt. He explained to me in detailed manner just how it affected him. Just then he grabbed his side and said: "Now it starts." He began to pray at the same time, with no relief, pain becoming more severe all the time. Finally, with no relief thru prayer he looked me squarely in the eye and said: "God d— it hurts."

Another time I was called to see a lady with distressing pains. She was in bed when I saw her. I asked her just what was the trouble. She stated that her adenoids hurt terribly. I had never heard any one complaining of adenoids hurting, so I asked here where it hurt. She looked at me rather bewildered and said: "Well in my rectum, of course."

Melvin P. Baken, Sr., M.D.

The jungle people of New Guinea, who are just emerging from a stone-age civilization including cannibalism, provided me with the most unusual problems. The lack of medical equipment and consultation in the area even further complicated their care. These people, however, seem to have remarkable recuperative powers and responded rapidly to basic treatment.

Ethiopia, which is an old civilization dating back to biblical times, proved most satisfying. In some of the remote mountain areas, people have not been influenced by modern civilization and live much as they have for centuries. Unusual cases included large ovarian tumors, intestinal parasites, leprosy, malnutrition; and brutal wounds from clashes between feuding tribesmen were common.

A particularly memorable moment for me occurred when I was given commendation and audience with Crown Prince Selassie, son of Haile Selassie, in his palace because of care which I rendered to a platoon of his bodyguards. They had been wounded near our village hospital when an ammunition store went off as a result of an overturned vehicle.

Paul G. Boman, M.D.

As I look back on the last fifty years I am most impressed by the privilege I have had of knowing intimately some of the great medical men who contributed so much stimulus and direction during my undergraduate years.

Three Doctors, Tuohy, Martin and Hirschboeck provided guidance and stimulation which encouraged me to visit different sections of the country and, later, Vienna and other European medical centers where I met many of the great teachers of that early period.

The clinical pathological conferences initiated by Dr. Tuohy in 1924 and the weekly Friday noon clinical conferences at the Clinic provided a continuing educational program. During this period we have seen the tremendous advance which has been made in the knowledge and treatment of disease. We have also seen a definite improvement in medical education and the development of excellent specialty training programs throughout the country. The association with later graduates who have joined our Group has alerted us to the progressive changes and procedures in medicine.

I am very proud of three sons. One son is Associate Professor of Secondary Education at the University of Minnesota, Duluth; another, graduated from the graduate program in Orthopedics at the Mayo Clinic, is now associated with the Duluth Clinic; and my third son is continuing his education in Specialized Education.

Earl J. Bratrude, M.D.

Born and raised in St. James, Dr. Bratrude after his medical education and a brief practice in Sacred Heart returned to practice in St. James. Doctor Bratrude, general surgeon, received his M.D. degree from the University of Minnesota. He interned at Minneapolis General Hospital and did postgraduate work at the Mayo Clinic. He served as president of the Watonwan County Medical Society in 1937.

Alex E. Brown, M.D.

Doctor Brown, internist, is noted for his early clinical studies on the use of sulfa drugs against bacterial-caused inflammation of the heart lining and acute bacterial meningitis. Moving to Rochester in 1925 as an assistant in medicine, he became head of a section of medicine and ultimately a senior consultant. Doctor Brown was born in Denver, Colorado, and received his M.D. degree from the University of Minnesota. He interned at Ancker Hospital and practiced in Stillwater from 1922 to 1925. He served consecutively as second and first vice president of the Association in 1951 and 1952. In 1951 he also was president of the Minnesota Society of Internal Medicine. Upon his retirement from the Mayo Clinic in 1963, Doctor Brown moved to Florida.

Philip W. Brown, M.D.

My contact with the Mayo Foundation and Clinic had its start in the Summer of 1919 when Dr. Wm. C. McCarty devoted much of his summer to teaching some eight to ten "eager beavers." Before leaving for my home, I applied for a fellowship in surgery.

My fellowship began September 1921, but after only a few weeks on a surgical service I transferred to the medical field. Under the excellent and patient guidance of Dr. A. H. Logan, L. W. Pollock, and L. A. Buie. I was soon battling the "G.I." problems. An interlude with Dr. John Stokes was of great value to me.

I struggled diligently—and futilely—to find some angle that would help to control such miserable and awful problems as chronic ulcerative colitis, regional enteritis, etc. The only dividend was the questionable selection for Sigma X.

The three plus years in service for World War II were spent in the warmer climate of New Guinea and Luzon. Since retirement, wife Elsie and I have travelled extensively. The celebration of retirement was a nine months' wandering "around the world."

And now, some ten years after retirement we have much to be grateful for. Three children and eleven "grands" make it seem worth while.

Oscar Engstrand, M.D.

The first 10 years of my practice were spent in rural Minnesota, the last five of which I was in charge of a 50-bed hospital in Warren, Minnesota. My principal and most challenging responsibility was performance of surgery for the doctors in the area.

Doing my own x-rays and diagnosis of the cases led me to a decision to take post-graduate study at the University of Minnesota and subsequently a move to Minneapolis. I established practice in the downtown area of Minneapolis in 1932 where I continued active practice until recently. The course of this experience first led to staff membership at the Swedish Hospital, and then to further post-graduate work at Chicago's Cook County Hospital.

This work led to membership in the American Society of Abdominal Surgeons. These affiliations made it possible for Mrs. Engstrand and me to attend the Abdominal Surgeons 1966 conference in Rome plus clinics in Paris and London.

Retirement has been mixed with travel to the southern areas in winter and summers at our homes in Wisconsin and Minneapolis.

Harold C. Habein, M.D.

Arriving at University Hospital, Minneapolis, in June 1920, having just been graduated from Harvard Medical School, one of the first persons to greet me was Dr. Moses Barron, a gentleman and an outstanding clinician and pathologist. My first paper* was written with Dr. Barron. It was the case history of a young child who died of lead poisoning from a face powder. The patient, I so well remember, was brought to University Hospital by Dr. W. W. Will of Bertha, Minnesota, an outstanding physician and for many years a driving force in the Minnesota Medical Associatoin. It was Dr. Barron's work on the ligation of the pancreatic duct in animals that came to the attention of Dr. Bantuig, resulting subsequently in the discovery of insulin. We were around before and after.

I went to the Mayo Clinic in 1923. There were only 65 doctors on the staff and there was only one building. It was a great privilege to know Dr. Will and Dr. Charlie personally. Goiter surgery was dangerous, carried out at high risk. One day Dr. Henry Plummer, a genius if there ever was one, announced that there would be no more goiter surgery until the patient had been prepared for surgery with Lugol's Solution. From that day on goiter surgery became a safe procedure. An early paper on goiter† was written with the help and permission of Dr. Plummer.

Pernicious anemia was often called "cancer of the blood," because patients died of it. The only treatment was whole blood transfusion which at best was only palliative. We had given blood transfusions to a patient with pernicious anemia on a number of occasions. Then for a year she had not returned to the clinic; but when she did return she appeared in the best of health and her blood was quite normal. When asked about her activities she stated that when she returned to her home on a farm near Wells, Minnesota, the men were "butchering hogs." A neighbor lady told her that she had heard liver was good for anemia. The patient said she liked liver and kept on eating it because she seemed to feel better. About two years after the above story, Dr. Waltman Walters and I went on a clinical trip to Boston. On arriving at the Peter Bent Brigham Hospital I found a number of old friends who were working with Minot & Murphy on a treatment for pernicious anemia. Swearing me to secrecy they told of feeding patients one-half pound of essentially raw liver each day. We saw the blood smears before and after. The rest is history.

Now, I am not able to tell my grandchildren of my military prowess, but I certainly can tell them how their grandfather missed the Nobel Prize.

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*Lead poisoning, with special reference to poisoning from lead cosmetics, Am. Jour. Med. Sc. 162. 833, 1921.

†The Management of Cases of Colloid Goiter Minnesota Med. 8:734-737 1925.

William A. Hanson, M.D.

Several years ago while looking through the "Family Bible" or geneology of the R. B. Stevens family, the name of Dr. Edward Jenner struck a bell with me. He was my father-in-law's grandfather and my wife's great grandfather. My father-in-law's associate was Mr. W. Fischer, the nephew of Joseph Lister, first baron, English surgeon.

Among other things this promepted us to spend the summer in England and on the Continent.

It was most interesting to see the name of Dr. Edward Jenner on the memorial marker in Westminster Abbey in London. We also visited St. George's Hospital in St. George's Square in London where the hide of the cow which had cow pox was hung on the wall of the "histological pathological laboratory" for display. In summary the four months spent in Europe were most pleasurable and rewarding for my wife, son, daughter—to say nothing of myself.

Victor P. Hauser, M.D.

Doctor Hauser is a native of St. Paul and was a general surgeon there. He attended Mechanic Arts High School and the University of Minnesota Medical School, graduating in 1921. After interning at Ancker Hospital, he established a private practice in St. Paul.

A. P. Lapierre, M.D.

Born in Minneapolis, Dr. Lapierre was graduated from St. Thomas College and from the University of Minnesota Medical School in 1921. He interned at St. Mary's Hospital, Minneapolis, and did postgraduate work in internal medicine in Vienna, Paris and London before beginning practice in Minneapolis.

Samuel N. Litman, M.D.

I came to America with my parents in 1909, at the age of 12, from Russia and settled in Duluth, Minn. There I completed my elementary and high school education, graduating from Duluth Central High School in 1915. Then I attended the University of Minnesota, graduating from Medical School in 1921. I earned my way by peddling newspapers and carrying newspaper routes while attending school, and set up bowling pins, sold books, and washed dishes to get through college.

After a one-year internship at Walter Reed Hospital, Washington, D.C., I set up general practice in Meadowlands, Minn. (1920 Census-Population-10), an extremely rural area at the time, practicing under the most primitive conditions until 1926. After spending some time in Pediatric Post Graduate Study, I returned to Duluth in 1927 and became associated with the Webber Hospital and Clinic as Pediatrician. I have been continuously associated with this group—later called the West Duluth Clinic.

In 1929, I married Miss Leone Silk, Duluth, and we have two sons.

I was Medical Director of the Scottish Rite Free Infant Welfare Clinics for 40 years and in 1948 was honored by the Euclid Masonic Lodge as the "Man of the Year" and in 1959 was named to Duluth's Hall of Fame for my work with the free baby clinics and work in city-wide polio clinics and for an immunization program at St. James Parochial School. This award is given on the basis of volunteer community service.

I always wanted to enter the Medical Profession because of the challenge it provided for service to humanity. I have enjoyed the practice of Pediatrics long enough to take care of some third generation children.

Thomas B. Magath, M.D.

Having spent my medical life in the laboratories of pathology, my most elucidative experiences relate to the role they have played in the practice of medicine. When I began my practice, laboratories were usually located in the basement or attic of the hospital or in any other undesirable place not wanted by other members of the staff. The Pathologist was truly the last man on the totem pole and his remuneration was generally about that of the janitor. Often he lacked staff status.

The main reason he was able to receive some tolerance, was the lurking fear he would discover some error of the internist or surgeon in the performance of a necropsy.

To be sure, the state of the art was such that his findings were often uncertain and the errors in his own tests were unknown and unsuspected.

All that began to change in the early twenties when pathologists founded their first learned societies and began seriously to develop themselves and the laboratory sciences. So successful has the process been that today the laboratory plays the predominant role in the diagnosis and control of treatment in all diseases. No physician can practice honorable, scientific, and legal medicine without its findings and opinions. Pathologists' incomes have advanced to the top brackets in medicine and they can now select the location they wish for their multiphasic laboratory. All this has given my fifty years in medicine full meaning and great satisfaction.

D. Morrison Masson, M.D.

Although as a young man my abiding interests were mathematics, classical studies and especially engineering, I was strongly attracted to medicine. I took my medical degree in 1920 from the University of Toronto and, after completing my internship, entered the Mayo Graduate School of Medicine in 1921 as a fellow, first in surgery but subsequently in medicine. After I was appointed to the staff of the Mayo Clinic in 1925, a long, happy and most satisfying tenure of ministering to the sick began and did not end until I retired in 1957. I believe that the privilege of elaborating and enhancing my own faculties in the stimulating ambience of a celebrated medical center was a rare one indeed, and I am happy also that my early affection for the classic achievements in other fields has never left me.

Lillian L. Nye, M.D.

A well-known St. Paul pediatrician, Dr. Nye, was chief staff physician of the child health clinics for the St. Paul Family Nursing Service. She also served as medical inspector for the St. Paul public schools as well as maintaining a private practice for over 40 years and serving on the faculty of the University of Minnesota Medical School. Doctor Nye was born in Zumbrota, Minnesota. Before entering medicine, she taught school at Featherstone and served on the chemistry faculty at the University from 1907 to 1915. She received her M.D. degree from Johns Hopkins University, Baltimore, Maryland.

Clinton F. Palmer, M.D.

Dr. Palmer has served Albert Lea as a general practitioner since 1924. He was born in Wisconsin in 1893 and was graduated from Rush Medical College, Chicago, Illinois, in 1921. He was licensed in 1923, opening his private practice in Albert Lea shortly thereafter.

Paul A. Robertson, M.D.

Born in Blackstone, Virginia, in 1892, Dr. Robertson attended Lynchburg College, Lynchburg, Virginia, and obtained his M.D. degree at the Medical College of Virginia, Richmond, Virginia. Doctor Robertson interned at Memorial Hospital, Richmond, before he opened practice in Lebanon Church, Virginia. Before moving to Austin, he practiced at Quincy Mining Company, Hancock, Michigan, for 11 years. While serving as physician in Austin, he also became its city health officer.

William H. Rucker, M.D.

I was raised in Montana by a father who drove cattle up the Chisholm Trail from Texas and a mother who came from Ireland. Though I received my medical degree from the University of Minnesota, I hoped to return to my native state to practice medicine. However, no rain, dust, grasshoppers, no crops and farm foreclosures brought me back to Minneapolis where I have spent these last fifty years: years in which I have greatly enjoyed the association with my conferees: years in which a few grim episodes have been greatly over-balanced by so many more happy and amusing happenstances that the smiles and laughs have swept the rocks out of the road. Now the memories of thankful patients and good friends and the sinking of a long putt blunts the question of a patient who asks "Are you still practicing?" or "How are you feeling?"

Peter S. Rudie, M.D.

Doctor Rudie gave all of his years of medical service as a surgeon to Duluth. Born in Blue Earth County, Doctor Rudie attended St. Olaf College, Northfield, and the University of Minnesota where he obtained his M.D. degree. He interned at St. Mary's Hospital, Duluth, and did postgraduate work at Cook County Hospital, Chicago, Illinois.

George N. Ruhberg, M.D.

Dr. Ruhberg practiced in St. Paul and served as president of the Ramsey County Medical Society in 1940. A neurologist and psychiatrist, Doctor Ruhberg received his postgraduate education at Harvard University, Cambridge, Massachusetts. He was born in Grafton, North Dakota, and received his M.D. degree from the University of Minnesota. Before attending Harvard, he interned for a year and a half at Ancker Hospital, St. Paul.

C. W. Rumpf, M.D.

I have been a practicing physician and surgeon at Faribault, Minnesota since 1922, member of the staff of Rice County District One Hospital.

My time in the armed services can be summed up this way: World War I, SATC, University of Minnesota. World War II, 1941-1946, Colonel, U.S. Army Medical Corps; ETO two years. Korean War 1951-1954. Member of Officers Reserve Corps, U.S. Army 1930-1962.

I received Old Shad's Citation of distinguished career and service to Shattuck School and Community, 1956; Faribault Chamber of Commerce, Distinguished Service Award, 1957; and Junior Chamber of Commerce Distinguished Service to Community, 1963.

I am the attending physician to Shattuck School and St. Mary's Hall, of Faribault, and I am also a Member Board of Trustees of Shattuck School.

A. Sach-Rowitz, M.D.

In looking back after a half century of medical practice past happenings seem too commonplace to mention. Practice accomplishments seem insignificant. This is probably as it should be, however, since knowledge itself is only a stepping stone to the attainment of more knowledge which can be secured only by continuing effort on the part of all of us who practice medicine.

I remember participating in civic affairs, in numerous medical organization activities, various service groups along with frequent medical meetings.

Cultivating associations with those in other lines of endeavor has been most rewarding. It has had a broadening effect on my thinking. I believe, and I am most grateful to those nonmedical associates for their influence.

Frances W. King Salmon

The most important years of my medical career were eighteen (1922-1940) spent on the mission field in China, helping to found a medical school for women. The most memorable among them were a year learning the language, philosophy and religion of China; four years as head of obstetrics at Margaret Williamson Hospital, teaching hospital of the Women's Christian Medical College; the teaching of physiology and pharmacology both there and to the men of St. John's University Medical School, Shanghai; and a year on the executive committee of the newly merged National Medical Association and China Medical Missionary Association.

The missionary physician, I discovered, needs to be a generalist and must learn to fashion his supplies from a tin can and a length of string, his drugs from a weed.

We saw ancient, often superstitious, sometimes wise traditions of the Chinese clash against the energy and medical progress of the West. Public health created special problems for government and medical societies in the Orient. I was aware of the great opportunities and need for research and the frustration of being prevented from following them by the more immediate pressure of clinical need.

We were so few and the problems so many. But the experience was a privilege and a challenge, and incomparably rewarding.

In the summer of 1932 I travelled on the Trans-Siberian Railway across Siberia, Russia, Poland, Austria, Bohemia and The Netherlands to England where I was married to Robert J. Salmon who was Professor of Biochemistry (on furlough). St. John's University Medical School and the Women's Christian Medical College, Shanghai. When I returned to China, we continued to teach in those medical schools.

In December 1940 the American Consular authorities in Shanghai strongly recommended that all American women and children should return to the USA because of the serious international situation. Traveling by the evacuation ship provided, I and my two daughters returned to Minneapolis where I joined the medical staff on the Glen Lake Sanatorium, on which I served until my retirement in 1962.

C. E. Sisler, M.D.

Medical costs and techniques and facilities have improved over the years, but my association with younger doctors and hospital staffs and nurses, proves to me that Tender Loving Care still counts most for the patient, in spite of increased pressure and specializations, though time with the patient seems limited.

Years ago one of my small sons got lost downtown, separated from his mother. When asked by an officer who picked him up what his father did, he replied "he fixes 'em," by way of identification. I'm happy and thankful for the privilege of still trying to "fix 'em," and hope I have given my patients the pleasure and satisfaction it has given me to serve them.

James J. Swendson, M.D.

On leaving the village of Amherst, Wisconsin, where I was born, I spent two years each at Lawrence College and at the Universities of Wisconsin and Chicago, after which I interned at the city hospital in St. Louis and later took post-graduate work at Washington University.

After practicing for a year with a surgeon in Appleton, Wisconsin, I moved to the friendly medical climate of St. Paul in 1922 where I have been happy in the practice of gynecology and obstetrics ever since.

One of my early interests was "twilight sleep" to relieve the pain of labor and I was an early advocate of routine episiotomy during delivery. Another interest has been surgical treatment of sterility due to blockage of the oviducts.

Medicine has advanced in our country since I started to practice. This has been impressed upon me by two recent experiences. One was a two months' service with Project Hope in Ecuador in 1964 where my local "counterparts" believed the only treatment for dystocia was cesarian section! They believed also that roast guinea pig was an excellent pièce de résistance for a dinner party!

The other experience was a medical tour of the communist countries with a party of forty Minnesota physicians in 1968 during which we appreciated the gracious hospitality of our hosts but were not always impressed by some of their medical practices.

As medical director of Planned Parenthood of St. Paul, I watched that organization develop into an important and respectable medical service.

The most gratifying project that I have participated in as chairman of the state medical associations committee on obstetrics, gynecology and maternal health for the past twenty-five years is the study of maternal mortality. We have acquainted physicians with our findings and we believe that our continuing study is an important factor in markedly reducing the number of deaths associated with pregnancy in Minnesota.

Dean Veirs, M.D.

Born on a farm near Mayview, Illinois, on March 16, 1885, I served the usual apprenticeship of a farm boy. I helped to take care of my little sister, feed the chickens, gathered the eggs, milked and herded the cattle. And while my mother and brother attended the evening weekly prayer meeting at our country church, I washed the supper dishes in the pan that stood on the wash stand just inside our back door and I dried the dishes on the roller towel.

Reaching school age (7) I walked 1½ miles to a little school house where nine pupils were the most that we ever had in attendance. Black man, anti-over and old sow were the games we played at recess and noon. If on the first day of school the new teacher came out and played with us, then we knew that SHE was a good teacher.

That glorious country life ended when I was 12 years of age. Mother was accidentally killed by a runaway horse. Taken by relatives, I worked during the summers and attended school until I finished high school. It was my desire to enter medical school but, being unable to locate $3000.00, I did what I thought was next best and entered University, graduating in Civil Engineering. For several years I worked for the Vincennes Bridge Company and the Great Northern Railway.

In 1917 I entered medical school and in 1921 at age 36 I graduated from the Medical Department of the University of Louisville, Louisville, Kentucky, took the Kentucky State Board and received my state license.

Promptly, I married next the finest woman that I have ever known, Dr. Ruby Jayne Smith. We both went to New York City for internships.

January 1, 1924, we began practice in St. Paul where we worked together for 40 years. Seven years ago we came to Hastings where I continued in practice.

Early in 1970 Dr. Smith-Veirs passed to her reward. On June 30, 1971, which would have been our 50th wedding anniversary, I retired at age 86.

And to both of us, over the years, it was a great satisfaction having been able to meet and try to help such fine grand people.

Waltman Walters, M.D.

Doctor Walters, internationally-recognized Mayo Clinic surgeon, was also known for his medical writing. His surgical publications number about 450 and for many years he was editor of "Archives of Surgery," a monthly publication of the American Medical Association. Since his retirement in 1960, he has published a book entitled "Reminiscences of a Mayo Clinic Surgeon, 1920-1960." Doctor Walters, born in Cedar Rapids, Iowa, was educated at Dartmouth College, Hanover, New Hampshire, and the University of Chicago, Chicago, Illinois. He interned at St. Luke's Hospital, Chicago, and took three years of postgraduate work in surgery at the Mayo Foundation. He was elected a member of the Leopoldian German Academy of Natural Sciences, which is devoted to the advancement of science in Germany, Austria and Switzerland. He was also elected a corresponding member of the German Surgical Society.

(Continued from Page 728.)

leagues should be immediately apprised of the fact that accreditation is not achieved by any "grandfather clause." It should also be noted that built into this certifying format was the requirement that every six years a family physician must redemonstrate by a certifying examination that he is qualified to maintain the status of Diplomate in the American Academy of Family Practice.

Presently, a general practioner may be allowed to take the certifying examination to become a specialist in family practice if he has successfully completed 300 hours of postgraduate study, and has limited himself to general practice for a five-year period. It should be noted that as of 1978, no physician will qualify to take the certifying examination unless he has successfully completed three years of a residency program in family practice.

I should hasten to add that although family medicine may be delivered by general practitioners, pediatricians, internists, general surgeons, obstetricians or others, family medicine as a discipline is of distinct character and should be treated as such in our medical education. It should be restricted to those physicians who choose to provide *comprehensive* and *continuous* care for all their patients regardless of sex or age. The new specialist in family practice is the only medical practitioner whose professional approach is based on something besides episodic and crisis orientation. He "marches to a different drummer."

The American Academy of General Practice and its Minnesota Chapter extends an open invitation to all members of the medical community to aid in increasing the number of practicing physicians. To that end, tutors, professors, patients, office personnel from the private sector must be made available to our medical educators and medical educational institutions. The tutorial system being evolved: the exposure of first, second, third and fourth-year medical students to clinical material in an office and hospital setting outside of teaching institutions is being demanded by the student as well as by the educator.

However, before we can obtain the cooperation of our colleagues in medicine, we must establish better methods of communication among physicians themselves. This requires a drastic change in attitude between the highly academic, research-oriented, specialty-organized medical institutions and the physician in the field. We can no longer defend the attitude of disconcern for public health, pollution, disrupted ecology, and political involvement, on the past platform of physician immunity. It should be noted that an uninvolved physician is involved by default.

We must also establish better public relationship withour patients and our lay press. To this end people must be made aware of the problems of physicians and the medical care delivery systems. It must be recognized that satisfactory communication cannot be achieved without favorable intercourse with the people we hope to serve.

We of the Minnesota Academy of General Practice through our national office have placed a high priority on and have expended thousands of dollars toward the development of good public relations. However, despite the progress made in our stated objectives, we are dissatisfied with our accomplishments. We need and humbly encourage the involvement of all members of the medical communtiy to further our goals in medical student and postgraduate education. We must also coordinate our efforts in development of better methods of delivery of first, second, and third-echelon medical care. An open invitation is again extended to our colleagues to assist in the development of better methods of communication among physicians and our medical community, and in establishing good public relations between the patient and his physician, enabling the doctor of today to continue in the free enterprise system of medical care and medical-care delivery.

E. P. Donatelle, M.D.
President
Minnesota Academy of General Practice

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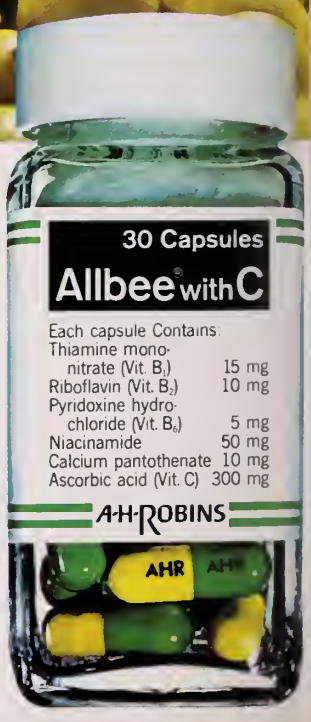


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Hypotonic Duodenography

R. E. ANDERSON, M.D.*

HYPOTONIC DUODENOGRAPHY is a radiographic method of evaluating the duodenum and the adjacent soft tissues without interference from duodenal peristaltic activity. It is indicated when regular upper gastrointestinal examination shows a questionable lesion of the duodenum, or when there is strong clinical suspicion of a lesion in this area despite negative findings on a routine upper gastrointestinal examination.[1,2,3,5]

Technique

The technique favored is essentially that of Bilbao et al.[1] With the patient sitting on the edge of the fluoroscopy table, his throat is partially anesthetized with a topical anesthetic, such as Cetacaine. A long tube with a Miller-Abbott tip is then passed through the nose to the stomach. The weighted tip of the tube is maneuvered to the pylorus under fluoroscopy. Peristalsis generally carries the tip of the tube through the pylorus and well into the duodenum in a matter of minutes.

At this point, approximately 30 milligrams of propantheline bromide (Probanthine) are given intramuscularly. A few cc. of barium mixture are then introduced into the duodenum via the tube in order to monitor the onset of hypotonicity in the duodenum. In three to five minutes, peristalsis in the duodenal loop usually appears minimal or absent.

With the patient's right side down (right posterior oblique) the atonic dilated duodenal loop is filled with barium, and fluoroscopic spot films are made at various angles. The patient is then changed to the left side down (left posterior oblique) position, and air is injected through the tube to provide a "double," or air-constrast pattern in the duodenal loop. Additional spot films are taken. In this manner, mucosal irregularities are well demonstrated, and masses indenting the flaccid loop appreciated.

Case Report

A 67-year-old male was admitted to University of Minnesota Hospitals with a two-month history of increasing fatigue and weight loss, and a one-month history of noticeable jaundice. He had had some diarrhea, and had noted light-colored stools. He had not experienced pain during this interval, however. Prior to the present illness, his health had apparently been good. Physical examination revealed jaundice and signs of weight loss. The right upper quadrant of the abdomen was not particularily tender and no definite mass was felt. Admission diagnosis was jaundice of uncertain etiology.

Laboratory data included a bilirubin of 13 milligrams percent total, with 7.5 milligrams percent direct. Other laboratory data suggested a combination of chronic liver disease and extrahepatic biliary obstruction.

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*Present address: Chevy Chase, Maryland.

An upper gastrointestinal examination was considered negative with the possible exception of a poorly defined filling defect along the medial aspect of the duodenal loop (Figure 1). Hypotonic duodenography was suggested. Air contrast films of the flaccid, dilated duodenal loop showed a mass lesion indenting the medial aspect of the duodenum (Figure 2a, b).

Surgical exploration revealed adenocarcinoma of the ampulla of Vater, a dilated common duct containing calculi, cholelithiasis, and biliary cirrhosis.

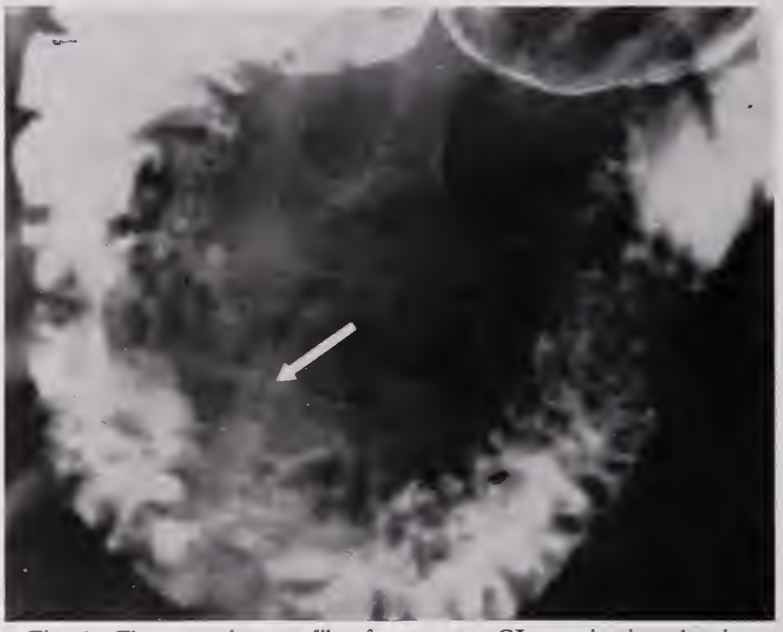


Fig. 1—Fluoroscopic spot film from upper GI examination showing a suspicious defect along the medial aspect of the duodenal loop (arrow).

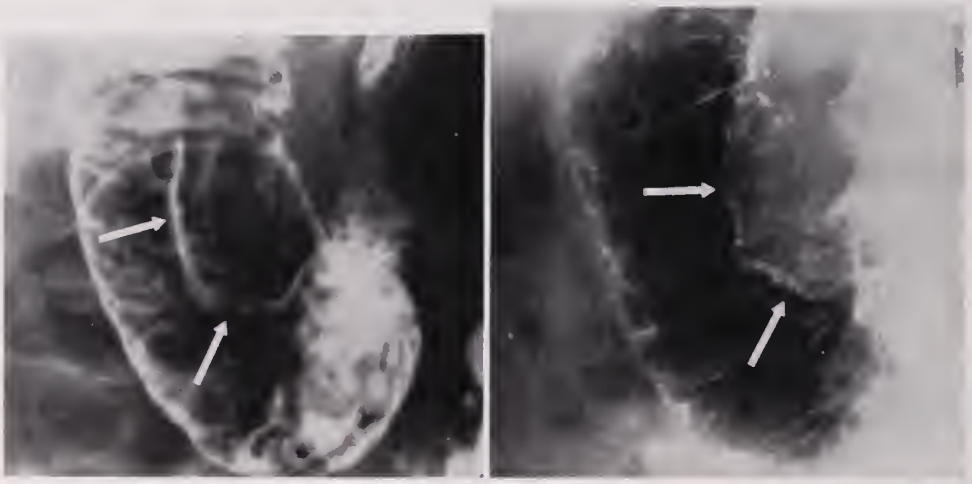


Fig. 2a (left) and 2b (right)—Spot films from hypotonic duodenography examination on the same patient showing a mass indenting the medial aspect of the duodenal loop (arrows.) (Tube was withdrawn into the stomach immediately prior to taking these views.)

Discussion

Lesions of the pancreas frequently defy definite diagnosis by upper gastrointestinal examination, isotope techniques or even selective arteriography. Because of the magnitude of the surgery involved in removal of a pancreatic neoplasm, it is important that such a mass lesion be demonstrated preoperatively if possible. Hypotonic duodenography offers an additional means of demonstrating a mass lesion adjacent to the duodenal loop using equipment available in any x-ray department. The procedure is safe and easily accom-

plished. If a patient cannot or will not swallow the tube, the examination can be done without the tube.[4]

Summary

Hypotonic duodenography is a radiographic method of examining the duodenal loop in a relaxed state, without interference from peristalsis or an overlying barium-filled stomach. It is indicated when a duodenal lesion is suspected on ordinary upper gastrointestinal examination, or when a mass lesion in the region of the ampulla of Vater or head of the pancreas is strongly suspected clinically. The method deserves wider application, particularly when exploratory surgery is contemplated.

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Medicine in the Seventeenth Century

Before Harvey, the liver was thought to be the central motive force of the blood, and blood was thought to move to-and-fro. Harvey became convinced that instead of going to-and-fro, blood goes around and around. This is very economical, since a little blood goes a long way, and people should be a lot more grateful than they are. He also thought the heart clenched and unclenched like a fist, though not mad about a thing. When Harvey published his findings, many refused to believe him and his practice fell off. Patients didn't want to go to a physician who had such crazy ideas. He might put a tourniquet around their neck to see whether it made them red in the face. But Harvey lived to see his ideas accepted. Living to be almost eighty helped.*

*Richard Armour: It All Started with Hippocrates, 1966.

Habits

When a timid soul engages in a flight from reality—when a person seeks to escape from the unbearable responsibilities of modern life—he most frequently decides (unconsciously) upon some type of digestive disorder as the most acceptable form of "liberating illness." All such "escapists" are willing to undergo all sorts of surgical operations. They are many times "all scarred up" like World War veterans. But surgeons are becoming educated. They are discovering that they cannot cut a pain out of the belly when that pain has an emotional origin . . . Surgical operations do not cure either anxiety neuroses or periodic emotional depressions.*

*William S. Sadler, Modern Psychiatry.





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Rhabdomyosarcoma of the Heart

S. SOCHOCKY, M.D.*

AMONG THE MALIGNANT tumors of the heart rhabdomyosarcoma is one of the most rare. The first case was reported by Escher[1] in 1909; 14 cases have been reported since. This report describes a further case which caused constrictive pericarditis.

Case Report

A 57-year-old white carpenter was admitted to the hospital. He developed a fever, general weakness, increasing shortness of breath, had a poor appetite, and had lost about 15 pounds during the previous six months.

Past History

He had never been seriously ill. There was no history of rheumatic fever, heart disease or contact with tuberculosis. The patient had smoked 20-30 cigarettes daily since the age of 16. His mother had died from myocardial infarction.

Physical Examination

On admission the patient was in chronic respiratory distress, with neck veins distended, cardiac impulse impalpable, heart sounds distant, no murmurs. Blood pressure—systolic 110 mm. Hg. over 80 mm. diastolic. Chest—percussion note was impaired and distant breath sounds were heard in right lower portions. Liver enlarged about four finger-breadths below costal margin; legs swollen. No clubbing of fingers or toes; no lymphadenopathy. Physical examination otherwise unremarkable.

Laboratory Data

Hemoglobin 12.5 grams per cent, white cell count 15,200, neutrophils 82, lymphocytes 17, monocytes 1. Urinalysis—specific gravity 1,020, albumin 3+, occasional red cells. Blood urea nitrogen 27 milligrams per cent, fasting blood sugar 126; total serum protein 7.3 grams per cent, albumin 2.5. Chlorides 86 mEq/liter, sodium 132, potassium 4.8. Total bilirubin 3.9 milligrams per cent, direct 2.8. Serum alkaline phosphatase 29.4 King-Armstrong units. Tuberculin skin test 1:2000 negative. Sputum negative for acid-fast bacilli on direct smear and no malignant cells found. Pleural fluid—clear, specific gravity 1,003, protein 2.7 grams per cent, red cells count 1,000, white blood cells 100, neutrophils 63, lymphocytes 34, monocytes 3. Lactic acid dehydrogenase 580 units. Pleural fluid showed cells suspicious of malignancy.

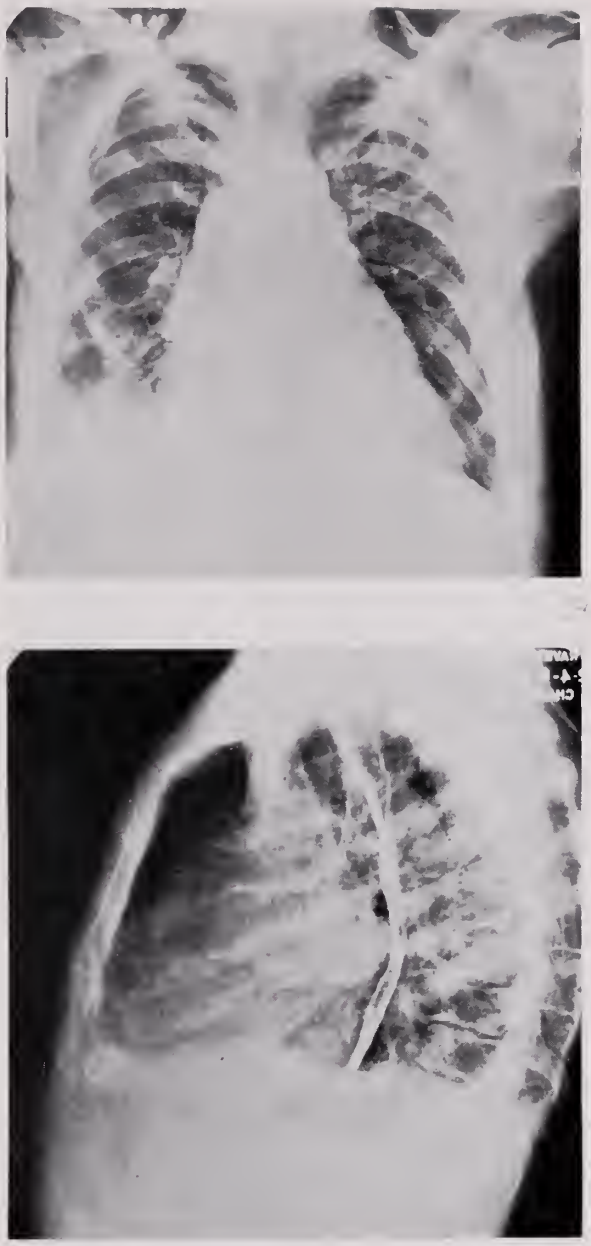


Fig. 1-a (top) and 1-b (bottom)—Chest x-ray 12,3,64, shows an enlarged heart. There is an irregular density in the right upper heart border and a density in right lower portion suggestive of pleural fluid. Right lateral chest film shows a small tumor mass around the hilum.

*Department of General Medicine, Veterans Administration Center, Sioux Falls, S.D.

Pleural biopsy showed an undifferentiated cell carcinoma. Pericardial fluid—clear, protein 1.3 grams per cent, red cells count 150, white blood cells 100, neutrophils 89, lymphocytes 11. No malignant cells found in fluid. Venous pressure 22-28 cm. of water. Circulation time, arm to tongue, 21 seconds (using Dexolin). Cardiac fluoroscopy showed decreased pulsation of heart in all segments. Chest x-ray showed an enlarged heart; a small density around the hilum and an opacity in right lower part suggested a pleural effusion (Figures 1a and 1b). Electrocardiogram consistent with a pericardial effusion and/or with a diffuse myocardial process.

Treatment

A presumptive diagnosis of carcinoma of the bronchus with metastases to heart was accepted. The patient received a low-sodium diet, digoxin, diuretics and repeated aspirations of right pleural cavity. He improved somewhat; however, he never responded well to treatment. He developed signs of cardiac tamponade and died suddenly on the 12th day after admission to the hospital.

Pertinent Autopsy Findings

Gross

There were approximately 650 ml. of clear, serous fluid in the right pleural cavity and approximately 500 ml. of similar fluid in the left pleural cavity, with only a few ml. in the pericardial cavity.



Fig. 2—Section of the heart shows it encased in a thick, firm, grey mass, with the pericardial cavity completely obliterated by the tumor.

The heart was encased in a thick mass of firm, grey-white tumor; the pericardial cavity was completely obliterated by tumor (Figure 2). Blunt dissection was required to separate the pericardium from the heart. The pericardium was 2.5 cm. thick in most areas. The weight of the heart plus the pericardial mass was 1380 gm.; the weight of the heart after the parietal layer of pericardial tumor was dissected away was 650 gm. The estimated weight of the heart without the tumor was 400 gm. A mass of tumor measuring 8 cm. in diameter was situated between the left atrium, pulmonary artery and ascending aorta (Figure 3). Tumor had invaded the outer wall of the pulmonary artery in one area.



Fig. 3—Photograph shows a mass of tumor measuring about 8 cm. in diameter, which was situated between the left atrium, pulmonary artery and ascending aorta.

Mediastinal lymph nodes, especially about the hila of the lungs, were enlarged and contained tumor; irregular masses of tumor were also present in the lower part of the mediastinum. Numerous tumor implants were present on the pleura, especially of the right lung, mostly over the lower lobes. The mediastinal surface of the pleura of the left lung was more affected than the lateral. A thick layer of tumor was also present on the diaphragmatic pleura and invaded the diaphragm.

Microscopic

Microscopically, the tumor was composed of

xtremely pleomorphic cells which varied great- in size and shape. Many giant cells with ingle or multiple nuclei were present. Some ells assumed "racquet" shapes, having a ta- ered body and an expanded end containing the ucleus. Occasional cells were "strap-shaped" vith two or more nuclei in tandem. The cyto- lasm was palely acidophilic and slightly gran- lar. Many cells had bizarre nuclei and large cidophilic nucleoli. Numerous longitudinal ibrils were easily demonstrated on phospho- ungstic-acid staining and a few cross-stria- ions found (Figure 4). In most areas where reticulin network was well developed, there vas a tendency for reticulin to surround indi- idual tumor cells. There was also a scanty mount of fibrous stroma which contained hronic inflammatory cells.

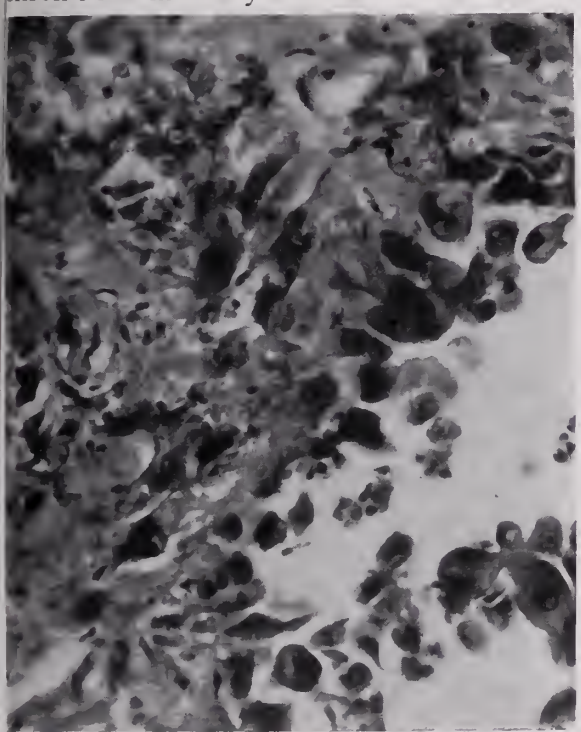


Fig. 4—Photomicrograph of microscopical slide shows pleomorphic cells, many giant cells with a single nucleus or multiple nuclei, some cells "racquet-shaped" and some "strap-shaped." Numerous longitudinal fibrils were demonstrated with phosphotungstic acid and a few cross-striations were found. Many cells have bizarre nuclei and large acidophilic nucleoli.

In many areas there was subepicardial invasion of the heart, involving both atria and both ventricles. Tumor extended along fibrous septa and was occasionally present between individual cardiac fibers; it also extended into the muscular trabeculae of the inner wall of the right ventricle. Only a few blood vessels were found to contain tumor. The tumor is an undifferentiated malignant neoplasm, but histologic features strongly suggest rhabdomyosarcoma. Each lung weighed 600 gm. A few fibrotic areas were present over the apical pleura bilaterally. There were also multiple, small pulmonary emboli. Tumor implants were present on pleura bilaterally; and in many areas alveoli contained erythrocytes, fibrin and siderophages. There was no tumor within the pulmonary parenchyma, no invasion of visceral organs other than the heart, also no other invasion of striated muscle than that of the diaphragm. Autopsy bacteriological cultures were negative.

Discussion

There are no pathognomonic signs and symptoms of rhabdomyosarcoma of the heart. This tumor may occur at any age, but more frequently in males. The common symptoms are shortness of breath, chest pain, fever, cough, loss of appetite and weight. Signs are variable, depending on size and location of the tumor. Pericardial involvement may be suggested by recurrent bloody effusion, signs of cardiac tamponade or constrictive pericarditis.

Myocardial involvement may be suggested by unexplained congestive heart failure, by various arrhythmias, or by conduction disorders. Involvement of the coronary arteries may cause coronary insufficiency, angina pectoris, or signs of myocardial infarction. Kahrs[2] described a rhabdomyosarcoma in an 80-year-old white female with heart failure which failed to respond to treatment. An electrocardiogram showed atrial fibrillation and changes suggesting myocardial infarction. Rhabdomyosarcoma involving endocardium may produce emboli, fever, and bizarre murmurs if valves are affected.

W. N. Dunnet[3] et al. reported a case of rhabdomyosarcoma which had been treated as subacute bacterial endocarditis. Blood cultures were negative and there was no response to antibiotics. Juan Z. Sta. Cruz[4] et al. reported a case of rhabdomyosarcoma in a child of eight years causing an obstruction of the mitral orifice. Longino[5] et al. described a rhabdomyosarcoma of the right ventricle occurring in a three-month-old infant. Leriche[6] et al. described a 53-year-old female with a presumptive diagnosis of dermoid cyst of the chest; a rhabdomyosarcoma of the heart was found on thoracotomy. Westad[7] reported a 24-year-old patient with a clinical diagnosis of a pri-

mary lung tumor; but an autopsy showed a rhabdomyosarcoma of the heart. Gordon Manson[8] et al. reported a rhabdomyosarcoma of the heart in a girl aged 12 with bilateral adolescent mammopathy as a presenting symptom. Clinically it was diagnosed as a lung carcinoma with possible metastases to the heart and pericardium. Pascuzzi[9] et al., in 1957, described a primary rhabdomyosarcoma in a 25-year-old female with hypertrophic osteoarthropathy. In this case diagnosis of primary rhabdomyosarcoma of the heart was made ante mortem by angiocardiography and periocardial biopsy.

In the case reported here, a presumptive diagnosis of carcinoma of the bronchus with metastases to the heart, mediastinum and pleura was made.

Primary rhabdomyosarcoma is usually found as a polypoid intracardiac mass or infiltrative type. Rhabdomyosarcoma of the heart is found frequently in the right side of the heart and often produces metastases to the lungs, pleura and mediastinum. A review of the literature revealed no convincing evidence of rhabdomyosarcoma metastatic to the heart.

Carcinoma of the breast and bronchus often produces metastases to the heart, lesions usually seen as small and discrete nodules within the myocardium.

Summary

Rhabdomyosarcoma was found as a tumor of 8 cm. in diameter situated between the lef atrium, pulmonary artery and ascending aort involving the pulmonary artery. The tumo was composed of extremely pleomorphic cell which varied in size and shape. Some cells ha a "racquet" shape, others were "strap"-shape with two or three nuclei. Numerous longitudi nal fibrils were easily demonstrated and a few cross-striations were found. The myocardium was the only striated muscle found to be in volved by tumor in autopsy. The muscles o extremities, thorax, back and abdomen were free of neoplasm, and there was no evidence o any other tumor in the body on autopsy.

Rhabdomyosarcoma of the heart may mimic almost any heart disease or tumor of the mediastinum or lung. Diagnosis may be obtained by clinical signs, symptoms and progress of the disease. Progressive cardiac failure refractory to treatment, unexplained arrhythmias, a recurrent bloody pericardial effusion, a progressive bizarre cardiac enlargement may arouse suspicion of malignancy. Roentgenographic electrocardiographic, angiocardiographic studies, pericardial aspiration, studies of pericardial fluid and pericardial biopsy will help in diagnosis.

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The Golden Age

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*The Patient's Progress, Edited by Felix Mardti-Ibanez, 1962.

Editor's Note: She probably had chronic, longstanding thrombophlebitis and eventual peripheral vascular arteriosclerosis. She was overweight; I bet she had hypertension.



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Book Report

Marijuana: the New Prohibition*

by
John Kaplan

He who fails to learn from the past is likely to repeat at least some of its mistakes. With that in mind, we might do well to consider now what may be useful in our own past experience with legislative sanctions against substance sale and use. The parallel between marijuana and alcohol is imperfect, but it is close enough to be helpful. It is, in fact, extremely helpful as used by Professor John Kaplan in his excellent book "Marijuana: The New Prohibition."

It is a scholarly and objective book, as one would expect from a professor of law at Stanford. But, as Professor Kaplan says, it is more than that. "This book . . . is not a mere academic exercise divorced from any passion. Although, like many Americans of my generation, I cannot escape the feeling that drug use, aside from any harm it does, is somehow wrong, I am deeply moved by the consequences of our present marijuana policy. As a lawyer and a teacher of law, I regard it as a matter of desperate urgency to repair the damaged integrity, credibility and effectiveness of our criminal law; and as one who is constantly in contact with students I am deeply upset by anything that increases their alienation from traditional American values.

". . . until I began my own study of the problem, it never occurred to me to ask more than whether the penalties for marijuana offenses were somewhat too stringent. It is easy to understand how, under the historical and social conditions in this country at the time, the emergence of a strange intoxicant such as marijuana might have been felt to justify the official and popular apprehension it received. Nor is it difficult to see why in such a situation the first reaction would be an attempt at suppression of the drug—especially since at the time the social costs of enforcing the law were so much less than they are today.

"Now, however, we have an increased familiarity with marijuana, from its wide use, from a more careful look at what has long been known about the drug, and from recent studies. Much more important, we are now aware of the enormous costs to our society of our present marijuana policy. I believe that we cannot delay facing this issue a great deal longer and that the only responsible course of action —indeed, in the long run, the only course of action available within the framework of a democratic society—is a liberalization of the marijuana law so extensive as to constitute an abandonment of the primary reliance on the criminal law in this area."

The book is actually the incidental result of Professor Kaplan's involvement in the preparation of a report to the Joint Legislative Committee to Revise the Penal Code of the State of California. The California legislature had voted to examine and overhaul its criminal laws and, because of the complexity of the task, decided that the initial drafting of new laws might best be done by a group of Reporters made up of professors of law at California's major universities. As his first major item of concern, Professor Kaplan was assigned the drug laws and studied them intensively. It soon became clear to him that the key current problem was the treatment of marijuana, and that until that problem was adequately handled there could be no significant progress in the broader area of drug abuse legislation in general. Thus, this

*World Publishing Company, New York, 1970.

book.

Professor Kaplan discusses thoroughly the role of marijuana as a symbol, noting that a major reason why the marijuana issue generates so much emotion both within families and in society at large is that the life-style and values that marijuana symbolizes to many people involve some of the most emotion-laden issues confronting the United States today. These issues include, he points out, the proper place of pleasure in our lives; the threat of radicalism, not only to our society but also to our values; the question of permissiveness and the proper degree of subordination of personal desires necessary to ensure survival of a civilized society; the necessity of obedience to authority, whether or not there is personal agreement with its commands; the issue of law and order, which not only includes respect for law enforcement in these difficult times but also has overtones of both crime in the streets and racial violence; and the strains caused by differing patterns of drug use, especially among those who, though not marijuana-users, have deep-seated worries about their own drug-taking patterns. He points out that the element of conflict between the culture of the young and that of the old makes it likely that marijuana will be seen as a moral issue, separate from the central practical considerations of societal costs and benefits of the marijuana laws.

He then uses the entire eighth chapter to demonstrate that it is impossible, if one thinks carefully about the matter, to regard marijuana as just a moral, as distinguished from a pragmatic, issue. And he notes the unfortunate emotional overlay of the problem which makes it difficult to think rationally about the issue at all. He discusses, and presents solid evidence concerning, the effects of marijuana, noting the frightful degree to which misinformation has been involved in crucial congressional hearings leading to passage of laws now on our books. He discusses the relationships between marijuana and dangerous drugs, devoting an entire chapter to that subject in general and another chapter to marijuana and heroin. He devotes another chapter to a consideration of marijuana and alcohol, then discusses marijuana control and the societal cost of marijuana laws. In the last chapter he discusses the future of marijuana criminalization.

Through the whole of this most excellent and timely book runs the fundamental theme: the wisdom of a law should be determined by weighing the costs it imposes upon a society against the benefits it brings to that society. The purpose of this book, as Professor Kaplans points out, is to apply this principal to the laws concerned with marijuana.

We, as physicians, are expected to be familiar with drugs of abuse in more than just their pharmacology. But the fact is now that, much as with Professor Kaplan before he set out on his in-depth study of drugs for his committee report, we simply are NOT expert regarding even marijuana. Far from it.

My belief, in submitting this review, is that we are not unwilling to do a little extra homework in acquainting ourselves better with the facts, even at this rather late date. The lay public and our elected legislators need informed input from physicians, and here in Professor Kaplan's book we have an excellent source of sound, objective, considered, in-depth information. The result of a reading of this book will certainly be a significant enlightenment—and, I frankly expect, a sharing of Professor Kaplan's conviction that our society must promptly remove at least its criminal sanctions against small-quantity possession and use of marijuana.

Robert Bjornson,M.D.*
St. Paul, Minnesota

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*Chief, Department of Radiology, St. Paul Ramsey Hospital and Medical Center.

Case Report

Acute Cholecystitis in a Child

JOHN B. RUTLEDGE, M.D.*

Review of the standard medical tests, including Christopher's Surgery, Mitchell Nelson's book on Pediatrics, and several others, showed that cholecystitis can be and frequently is found in the very young, and gallstones have been reported in newborn infants. However, these stones are generally associated with febrile diseases.

Case Report

On the afternoon of July 22, 1969, a five-year-old white male was brought to our office by his mother and father. He had awakened about 2 a.m. with pain in his abdomen and a chill. He then went back to sleep and slept until six o'clock. When he awoke at that time pain was again present and persisted throughout the day, although it was not particularly severe, and he felt rather cold all morning. He vomited juice in the morning and ice cream at noon. He was tender in the right abdomen just above the umbilicus and by 3 p.m. a mass was palpable in this area. Heat to his abdomen had relieved the chill but had not relieved the pain.

Past History

The child was born of a full-term delivery. The mother felt that it was probably an instrument delivery, but she was not certain. As an infant he had had the usual immunizations, and his mother felt that he may have had a few more abdominal complaints than her other children.

Family History

The father, 46, and the mother, 41, are both living and well with no gall-bladder disease. The patient has five brothers and five sisters between the ages of 21 and two years. All are living and well; none of them have ever had gall-bladder disease. His maternal grandmother, a maternal aunt, and a maternal uncle all have had cholecystectomies—the aunt at the age of 22.

Physical Examination

The child was well oriented, in no acute distress, but obviously suffering some pain. The examination was negative throughout except for the findings in the abdomen.

The abdomen was tender in the right upper quadrant with a palpable mass in the subcostal area which seemed to be the point of maximum tenderness. There was no rebound tenderness and no distention. Bowel sounds were normal.

Laboratory work on admission: hemoglobin 11.2 grams percent; WBC 14,900; differential: 13 bands, 77 segs, 9 lymphs, and 1 mono. Urinalysis: PH 5, specific gravity 1.023, trace of albumin, and occasional red blood cells.

It was decided that the patient required surgery and he was taken to the operating room at approximately 5 p.m. with a presumptive diagnosis of probable appendicitis and a secondary diagnosis of intussusception. We commented at the time that if the patient were older—say 11 or 12 and were a girl, we would think strongly of cholecystitis because of the palpable mass which felt somewhat like a gall bladder in a young child. Through a right paramedian incision the mass was indeed found to be the gall bladder, which was very tense. The wall was thickened and the bladder would not empty. No stones were palpable. The liver, the stomach and duodenum, the transverse and ascending colon, and the appendix were all normal. There was no Meckel's diverticulum.

A cholecystectomy was done without incident, together with an incidental appendectomy and a liver biopsy. Postoperatively the patient had some nausea which was controlled with nasogastric suction. Bowel sounds were audible on the evening of the second postoperative day. The nasogastric tube was removed on the fourth postoperative day and he continued to improve. He left the hospital in good condition on the ninth postoperative day.

Postoperative Studies

Laboratory

Because of the unusual nature of the case and the fact that such cases are frequently associated with febrile illnesses, the following laboratory work was done postoperatively: Agglutinations for salmonella typhi and paratyphi and for brucellosis were reported as negative. Cold agglutinins were also negative, and the patient had a negative red cell fragility test.

Pathology

The pathology report noted acute and chronic cholecystitis without cholelithiasis. The liver biopsy showed some hepatitis, but the pathologist felt that this was due to the fact that the section had been taken from a segment close to the gall bladder. Grossly the liver appeared normal, and the patient did not run a

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course comparable to that of infectious hepatitis. The appendix was negative.

Conclusion

This is a case of a five-year-old white male with acute and chronic cholecystitis without stones, not associated with any of the usual conditions in which cholecystitis is found in the very young. Cholecystectomy was done together with liver biopsy and incidental appendectomy. The patient made a normal postoperative recovery.

We have continued to follow the patient, and it is now 15 months since his surgery.

Cholecystitis can occur in the very young and should be considered as a possible diagnosis, particularly if there is a mass palpable in the right upper quadrant. Cholecystectomy can be performed on a child without any apparent ill effects.

It's The Law

Requirements Before Results of Blood Test May Be Admitted

Considerable controversy has arisen as regards blood samples tested for blood alcohol. The admissibility into court of blood alcohol determination is subject to a number of stringent regulations. A recent ruling by the Iowa Supreme Court set forth regulations in such case.

The Iowa Supreme Court ruled that (1) the blood sample was timely taken, (2) it was taken from a particular identified person, (3) it was taken by an authorized licensed physician, medical technologist or registered nurse designated by a licensed physician, (4) the instruments used were sterile, (5) the blood taken was properly preserved or kept, (6) it was labled, (7) if transported or sent, the methods and procedures used in the transporting or sending must be acceptable, (8) the methods and procedures used in conducting the test must also be acceptable, and (9) the identity of the person or persons supervising the tests must be approved.

Withdrawal of blood from the body of the person accused of a crime is a serious matter, although constitutional. If the above rules are followed, and adequate and proper foundation is laid, the blood alcohol sample should be admissible into court as evidence.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Cart Before The Horse

*A fellow told me the other day they have a "wonder drug" up at the Mayo Clinic, so new they haven't even got a disease for it yet.**

*Maxwell Droke: Speaker's Handbook of Humor.

Every sin is the result of a collaboration.—Stephen Crane

Thrombus Formation on Polymeric Materials

V—Effect of Interface on the Formed Elements

HAROLD D. KLETSCHKA, M.D.† and DOUGLAS A. OLSEN, Ph.D.*

THE PRECEDING ARTICLES have considered the clotting of blood primarily from the point of view of blood proteins interacting with vascular or polymer interfaces. The formed elements also interact with surfaces and, in doing so, cause alteration of plasma proteins. Thus, in order for a surface to be truly non-thrombogenic, damage to the formed elements must be minimal.

The various effects on the formed elements are discussed separately in this section; however, the inter-relationship is complex. To illustrate this point: Differences in aerobic metabolic rate of pumped blood (primarily red cells) indicate that cellular and plasma damage and involvement can occur beyond simple destruction of the cellular elements.[2] Alterations in pH and electrolyte concentrations occur when blood is exposed to a foreign surface.[1] Collection of blood in glass results in damage, not only to the platelets, but to the white blood cells as well. These cells are readily fragmented and agglutinated when sedimented in ordinary glassware.[2] Physical factors, including foreign surfaces, weaken or destroy platelets, leukocytes, and red cells.[3]

While some of these effects may be induced mechanically (such as rupture of macromolecular chains during shear), it is believed that most are due to surface contact with the wall of the device being used. It is conjectured that some of the adverse side effects noted by the use of the artificial kidney may result from some of the longer-range material-blood interactions just cited. Some of these side effects include peripheral neuropathy, severe anemia, mild gout, malaise, and irritability.[4]

Red Blood Cells

Hemolysis

Destruction of red blood cells has been used as a standard guide to measure the traumaticity of various pumping systems used in artificial heart devices, heart-lung machines, or other similar applications. Although destruction as measured in such systems was once considered to be due principally to mechanical effects, it is now known that the effect of the interface on the red blood cells may be of paramount importance. As noted above, the work of Bernstein et al.[5,8] and of Blackshear et al.[9] indicated that the hemolysis of red blood cells is due primarily to the interaction of the red cells with the wall of the vessel or pump. They found that hemolysis is proportional to the square of the rate of red cell-wall collision.

Bernstein and Gleason[8] have discussed the importance of polymeric interfaces in the causation of hemolysis. They pumped canine blood under conditions where tubing dimensions, surface areas, flow rate, and average velocity were controlled. Four types of tubing were tested, viz., Silastic, Tygon (polyvinyl chloride), GBH-Tygon, and latex rubber. Changing the pump settings from barely nonocclusive to just occlusive positions increased hemolysis from four to 26 times with Tygon tubing and to a lesser degree with both GBH-coated Tygon and latex rubber. However, when both occlusive and nonocclusive settings were compared using Silastic tubing, there was somewhat less hemolysis with complete occlusion. The authors felt the evidence pointed strongly to the nature of the surface, and of cell-surface interactions in the development of the experimentally produced

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Reprints may be obtained at the end of this series from Dr. Olsen at 4106 Linden Hills Blvd., Minneapolis, Minnesota 55410.
See page 773 of July issue, page 877 of the August issue, and page 989 of the September issue, 1970, and page 635 of the July, 1971 issue.

hemolysis. They felt that the results were related to chemical or physical aspects of the tubing materials, and cited such tubing characteristics as stiffness, elasticity, surface roughness, and wettability as some of the properties which might have contributed to the findings. It was of interest that in their tests GBH-coated Tygon, which has been shown to carry a negative surface charge, failed to reduce surface effects causing hemolysis. In fact, they discovered that the *in-vitro* hemolysis was twice as great when this coating was employed. Since it appeared unlikely that a heparin lining would be chemically damaging to red blood cells, the authors postulated that increased surface roughness in the coated tubing was probably responsible for the increased hemolysis. Latex rubber, which proved to be the most hemolytic material, was grossly the roughest of the materials tested.

Somewhat at variance with the findings cited above is the work of Kusserow and Kendall[10] who tested the fate of blood circulated passively in circular loops of Tygon tubing. They found that: (1) the rate of hemolysis increased as the shear stress increased, (2) increasing values of Reynold's number for a tubular system may actually be attended by a decreasing rate of hemolysis, (3) a decreased radius of curvature resulted in increased hemolysis, and (4) the pronounced lowering of the leukocyte count so frequently observed in perfusion systems containing pumps and oxygenators was not observed. It should be noted that the tubes were only half filled with blood so that a blood-air, as well as a blood-polymer interface existed. Blood-air interfaces, as discussed in a previous section, cause deposition of protein films and adhesion of platelets. Blood-air interfaces may also be a factor in hemolysis.

Indeglia et al.[11] state that the mechanical destruction of red blood cells may be due to forces associated with pressure, shear, turbulence, and red cell-wall interactions. Studies done by this group showed that shear and pressure played minor roles in red cell destruction. Their studies demonstrated that red blood cell damage occurs at or close to the blood-wall interface and is dependent upon interactions between the red cell and wall surface. Turbulence seemed to be of importance in increasing hemolysis by increasing the transport of red cells to the wall. Rafferty, Kletschka et al.[12-15] designed artificial heart pumps which decreased the number of red blood cell-wall encounters per given period of time and were able to pump blood up to six hours even at high flow rates without detected red blood cell destruction. Earlier work by Bucherl[16] and Stewart and Sturridge[17] also indicated that the extent of destruction varies with the material of which the tubing and the pump-oxygenator parts are made, and that, in general, the smoother the walls, the less the hemolysis.

Hirose et al.[18] described differences in the amount of hemolysis produced in tubing made of different plastics and noted enhancement of hemolysis after ethylene oxide sterilization. Koller[19] has stated that hemolysis is also dependent on the origin (manufacturer, process, etc.) of the polymer. Leaching of hemolytic agents out of polymeric tubing has been reported by Keith et al.[20]

Electrical Charge Effects

The following study by Sawyer et al.[21] deals with metal surfaces; however, it shows the influence of electrical charge on human red cells. Sawyer et al. were principally concerned with the relationship of erythrocytes sticking to the metal surface with electrical potential. For tin, iron, cobalt, nickel, titanium, and copper they found that the sticking potential became more positive in more alkaline solutions. They pointed out that erythrocytes are negatively charged in neutral solutions so that with a neutral pH the red blood cells will tend to stick to a positively charged surface. Although the surface charge density of human erythrocytes is rather precisely known[22], the chemical nature of the exposed parts of the cell wall is open to question. Inasmuch as Sawyer et al.[21] found that the interaction takes place at potentials more positive than a critical value, it appears that an oxidative process must be involved with the subsequent formation of a bond between the cell membrane and the metal surface. They felt that the structural proteins of the cell membrane are probably involved, since experiments with erythrocyte ghosts and platinum electrodes showed sticking at the same potential as for in-

act cells. Unlike many of the phenomena encountered in blood-interface studies Sawyer's observations have been interpreted at the molecular level and are worthy of discussion.

The complexes occurring between active groups in proteins and metal cations have been very extensively studied.[23] The principal complex-forming sites in proteins are carboxyl, amine, and sulfhydryl groups.[21] In general, sulfhydryl groups are considerably more active in this respect. Studies of the interaction of chloromerodrin, parachloromercuribenzoate, and parachloromercuribenzenesulfonate with both intact cells and hemoglobin-free ghosts have shown that about 1 to 1.5 percent (i.e., ~ 1 to 1.5 $\times$ 10^6 sites per cell) of the total stromal sulfhydryl groups are outside the diffusion barrier normally imposed by the membrane of the intact cell.[24] Christian et al.[25] made polarographic measurements on whole mitochondria and mitochondrial ghosts and found the typical anodic waves associated with oxidation of sulfhydryl groups in cysteine. Although there is now a reasonable amount of information on the electrode behavior of oxidation-reduction polymers,[26] very little of it relates to functional groups containing sulfur. There is evidence that E_o values for all the thiodisulfide systems studied so far are similar to within 0.1 volts or so. In cases where the sulfhydryl groups occur in a large molecule, steric considerations may prevent the reaction from going beyond the intermediate stage of a radical bonded to a metal surface. Sawyer et al.[21] propose this as the mechanism by which erythrocytes are bonded to platinum, gold, carbon, silver, nickel, and mercury at potentials more positive than +0.3 volts.

These same investigators observed that the more active metals, tin, iron, cobalt, titanium, chromium, and copper, exhibit sticking of erythrocytes over a range of more negative potentials. They believe this phenomenon may be due to (1) the anodic current flow being sufficiently large to cause the erythrocytes to migrate and be held at the surface by electrophoresis or (2) ions of readily variable valency (e.g., Fe, Cu) act as catalysts in the oxidation of cysteine by molecular oxygen.

Leukocytes

Variations in Count

Many investigators have observed a decrease in the leukocyte count during artificial circulation.[27-31] Kolff et al.[32] noted an absence to slight increase in the white blood cell count during extracorporeal circulation. All the above investigators reported an increase in the white count following their perfusions. The fact that this increase in the leukocyte count occurs after the conclusion of perfusion was found by Brinsfield et al.[33] to be due to the fact that the perfusions had been of short duration because, when the perfusion time was extended, the rise in the white count occurred during the period of artificial circulation. The initial decrease in the white count is principally at the expense of mature granulocytes and mononuclear cells, and the subsequent rise is due mainly to an increase in the immature granulocytes. There is no conspicuous change in the number of eosinophiles.[3] The protective effect of an appropriate interface has been shown by Kusserow and Kendall[10] who found that the white blood count remained unchanged for periods up to 100 minutes when blood was circulated passively in Tygon tubing.

Chemotaxis

The phenomenon of chemotaxis characterizing the function of these cells is a process which causes the leukocytes to move in directions governed by *chemical substances* emanating from *foreign particles* or products set free when tissues are injured. Thus it would not be surprising to find the leukocytes sensitive to the foreign surfaces to which they might be exposed (chemotaxis has not been observed with lymphocytes).[34]

Phagocytosis

The mechanism of phagocytosis relates intimately to the fundamental properties and functions of the leukocytes. Neutrophils engulf and destroy bacteria and small particles, and the monocytic series of cells characteristically engulf not only bacteria but also protozoa, particulate matter, and even red cells.[34] Phagocytosis is thought to represent an interplay of surface forces and is accompanied by

a spontaneous decrease in the free energy of surfaces.[35] These properties of phagocytosis suggest that the leukocytes would be responsive to interfacial properties.

Damage to Leukocytes

Gravel et al.[36] noted the adherence of white blood cells to the plastic walls of an extracorporeal circuit. Kusserow et al.[37] stated that prolonged blood pumping under the conditions of a perfusion system may inflict damage on leukocytes as well as erythrocytes. Kusserow measured leukocyte oxygen utilization before and after extended *in-vitro* perfusion in a pump circuit and found distinct decreases in 13 of 15 blood samples, most in excess of 60 percent. He noted that such pumping inflicts a fundamental metabolic derangement upon leukocytes as expressed by decreased respiratory activity in those cells. The perfusions were done with a closed loop system utilizing polyvinyl chloride tubing in which a roller pump was used to propel the blood. His group also detected morphologic changes in some leukocytes which were both nuclear and cytoplasmic in nature. Nuclear changes included distortion of granulocyte lobes, hyaloid transformation, homogenation, and irregularity of nuclear contour with occasional vacuolization. The experiments were performed at room temperature over a 16-hour period, and blood for the experiments was obtained under sterile conditions.

The destruction of platelets and leukocytes in this fashion has more far-reaching effects than their own destruction, since alterations of the plasma proteins unquestionably result from platelet damage and very likely also from the lysis of leukocytes.[2]

Platelets

Platelet Adsorption

Platelets have a tendency to agglutinate into masses and to form deposits upon any roughened surface of foreign material;[38] microirregularities appear to act as sites for adhesion.[39] Decreased platelet counts are consistently seen after open-heart surgery, with good evidence that platelets are sequestered and lost in the extracorporeal system in such cases.[40,41] Wall-bonded heparin minimizes prosthetic thrombosis by blocking the agglutination of platelets in addition to other factors.[42] Lyman et al.[43] carried out platelet adsorption studies utilizing "open" or "static" cells and "closed" cells. In the latter cells a blood-air interface was not present. Open cells gave up to 10 times as much platelet adsorption as closed cells. Platelet adsorption appeared to bear no direct relationship to the platelet count in the blood; therefore, adsorption was felt not to be related to collision frequency with the surface. There were significant differences in adsorptivity of platelets by different polymer surfaces, and the data plotted as a function of critical surface tension show a steady increase with that parameter; this relationship is at least qualitatively similar to the critical surface tension-coagulation time plot discussed previously. Platelet adsorption in closed cells is reduced or almost entirely eliminated when the polymer surface, either Teflon FEP or Silastic, carries a monolayer of adsorbed albumin or fibrinogen. It also appeared that adsorption of the platelets onto the surface was a random process and competitive with the plasma proteins. Lyman and associates concluded that platelet adsorption increases with critical surface tension, which in turn is related to surface thrombogenicity. Blood platelet adsorption, according to Lyman, is the primary requirement for clotting.[44]

Platelet Degradation and Adhesion

Once adsorbed, disruption of the platelets or their degradation may then trigger activation of Factor XII. Although some evidence exists that a negative net charge of about 0.4 v at the surface of metals prevents platelet adhesion and certain forms of coagulation,[45] a charge of 2.0 v is needed to cause thrombosis, or possibly a mere precipitation of proteins locally[46], and will damage the endothelium itself;[47] even mild injury of the endothelium can liberate adenosine diphosphate and thus cause adhesion of platelets.[48] The interaction of platelets with surfaces is perhaps the most important stimulus in the initiation of thrombosis.[49-51] Adherence of platelets to surfaces can lead to release of their constituents, which include serotonin and nucleotides such as adenosine diphosphate (ADP).[51-53] The re-

eased adenosine diphosphate causes platelet ggregation and is thus important in the de- elopment of the platelet mass.[54,55] By these nechanisms the stimulus provided by contact vith an appropriate surface is able to produce i platelet mass without the participation of blood proteins.[49]

Compounds which inhibit platelet surface reaction *in vitro* also have a significant effect on thrombus formation *in vivo*.[49] Two such drugs are acetylsalicylic acid and sulfinpyrazone. Destruction of platelets, as well as a change of platelet adhesiveness, has often been noted in extracorporeal circulation. These may be due to phospholipid adsorption, to protein denaturation or to actual cellular breakdown caused by surface contact in the external circuit.[56-59]

Platelet adhesion to a foreign surface appears to correlate with the surface energy,[43] and the findings have carried an interpretation that decreased platelet adhesional lifetime occurs on lower energy surfaces.[60] The number of platelets adsorbed on a surface has been disputed as being related instead to the thrombogenicity of the surface.[60] It has been observed that initial attachments of platelets on the surface were essentially identical on glass and polyurethane, but aggregation and formation of a thrombus was less definite on polyurethane as compared to glass.[60]

The thrombocytopenia which has been repeatedly demonstrated to occur during extracorporeal circulation is generally believed to result from platelet deposition on foreign surfaces or any activation of the coagulation system, and distinct differences were found between various oxygenators tested in their ability to produce thrombocytopenia.[61] A decrease in the platelet count of the order of 50 to 70 percent is a consistent finding during extracorporeal circulation.[3] Thrombocytopenia in such instances results from platelet deposition on foreign surfaces.[62]

Other Effects

Enzymes and other substances liberated by cell or protein degradation during extracorporeal circulation may cause vascular disturbances and impair the coagulation mechanism.[3] Stephenson et al.[28] reported an average decrease in plasma protein levels of 1.4 gm percent, primarily at the expense of the albumin fraction. Considerable change in the electrophoretic distribution of lipoproteins has been noted.[63] Gadboys et al.[64] found that heparinized blood is unaffected by severe agitation; yet, other authors have reported decreases in fibrinogen values ranging from 5 to 50 percent after extracorporeal circulation.[29,65] Because of the ease with which protein is adsorbed onto foreign interfaces it seems likely that the observed changes are due, at least in part, to such an interaction.

Denaturation of plasma proteins has also been reported as a cause of morbidity and death after intracardiac operations using extracorporeal circulation.[66] While some of this results from interaction at the gas-blood interface in oxygenators, denaturation of proteins can occur almost as readily at the material-blood interface. Denatured proteins may contribute to long-range allergic or hypersensitivity reactions.[4] Intravascular sludging has also resulted from extracorporeal circulation,[67] and this change of viscosity would appear to be a result of protein denaturation.[4]

Summary

In this and the previous articles of the series, we have discussed the recent literature as it pertains to interactions of blood proteins and platelets with polymer surfaces. The nature of blood-polymer interactions is exceedingly complex and far from being completely understood. Added complexities are the related problems of damage to the formed elements. Such damage is a secondary effect, since thrombus formation is initiated principally by blood proteins and platelets. However, for a surface to be truly non-thrombogenic, damage to the formed elements must also be minimal.

References may be secured from the author or the reprints.

One of the hardest things for any man ot do is to fall down on the ice when it is wet and then get up and praise the Lord.—Josh Billings.

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Contraindications: Known hypersensitivity. Should not be given concomitantly with or within at least 14 days following the discontinuance of a monoamine oxidase inhibitor. Then initiate dosage of amitriptyline HCl cautiously with gradual increase in dosage until optimum response is achieved. Not recommended during the acute recovery phase following myocardial infarction or for patients under 12 years of age.

Warnings: May block the antihypertensive action of guanethidine or similarly acting compounds. Should be used with caution in patients with a history of seizures or urinary retention, or with narrow-angle glaucoma or increased intraocular pressure. Patients with cardiovascular disorders should be watched closely; arrhythmias, sinus tachycardia, and prolongation of the conduction time have been reported, particularly with high doses; myocardial infarction and stroke have been reported with drugs of this class. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Safe use during pregnancy and lactation has not been established; in pregnant patients, nursing mothers, or women who may become pregnant, weigh possible benefits against possible hazards to mother and child.

Precautions: When used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated; in manic-depressive psychosis, depressed patients may experience a shift toward the manic phase, and paranoid delusions, with or without associated hostility, may be exaggerated; in any of these circumstances, it may be advisable to reduce the dose of amitriptyline HCl, or to use a major tranquilizing drug, such as perphenazine, concurrently.

When given with anticholinergic agents or sympathomimetic drugs, close supervision and careful adjustment of dosages are required. May enhance the response to alcohol and the effects of barbiturates and other CNS depressants. The possibility of suicide in depressed patients remains during treatment and until significant remission occurs; this type of patient should not have easy access to large quantities of the drug. Concurrent electroshock therapy may increase the hazards of therapy; such treatment should be limited to patients for whom it is essential. Discontinue the drug several days before elective surgery if possible.

Adverse Reactions: *Note:* Included in this listing are a few adverse reactions not reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each reaction be considered when amitriptyline is administered.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms. *Anticholinergic:* Dry mouth, blurred vision, disturbance of accommodation, constipation, paralytic ileus, urinary retention, dilatation of urinary tract. *Allergic:* Skin rash, urticaria, photosensitization, edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, parotid swelling. *Endocrine:* Testicular swelling and gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido. *Other:* Dizziness, weakness, fatigue, headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, drowsiness, jaundice. *Withdrawal Symptoms:* Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise; these are not indicative of addiction.

How Supplied: Tablets containing 10 mg and 25 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100, 1000, and 5000; tablets containing 50 mg amitriptyline HCl, in single-unit packages of 100 and bottles of 100 and 1000; for intramuscular use, in 10-cc vials containing per cc: 10 mg amitriptyline HCl, 44 mg dextrose, and 1.5 mg methylparaben and 0.2 mg propylparaben as preservatives.

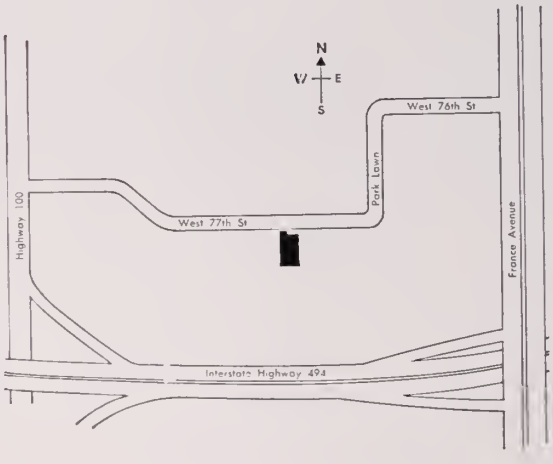
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Pre-Sate (chlorphentermine hydrochloride) is indicated in exogenous obesity, as a short term (i.e. several weeks) adjunct in a regimen of weight reduction based upon caloric restriction.

Contraindications
Glaucoma, hyperthyroidism, pheochromocytoma, hypersensitivity to sympathomimetic amines, and agitated states. Pre-Sate (chlorphentermine hydrochloride) is also contraindicated in patients with a history of drug abuse or symptomatic cardiovascular disease of the following types: advanced arteriosclerosis, severe coronary artery disease, moderate to severe hypertension, or cardiac conduction abnormalities with danger of arrhythmias. The drug is also contraindicated during or within 14 days following administration of monamine oxidase inhibitors, since hypertensive crises may result.

Warnings
When weight loss is unsatisfactory the recommended dosage should not be increased in an attempt to obtain increased anorexigenic effect; discontinue the drug. Tolerance to the anorectic effect may develop. Drowsiness or stimulation may occur and may impair ability to engage in potentially hazardous activities such as operating machinery, driving a motor vehicle, or performing tasks requiring precision work or critical judgment. Therefore, such patients should be cautioned accordingly. Caution must be exercised if Pre-Sate (chlorphentermine hydrochloride) is used concomitantly with other central nervous system stimulants. There have been reports of pulmonary hypertension in patients who received related drugs.
Drug Dependence Drugs of this type have a potential for abuse. Patients have been known to increase the intake of drugs of this type to many times the dosages recommended. In long-term controlled studies with the high dosages of Pre-Sate, abrupt cessation did not result in symptoms of withdrawal.
Usage In Pregnancy The safety of Pre-Sate (chlorphentermine hydrochloride) in human pregnancy has not yet been clearly established. The use of anorectic agents by women who are or who may become pregnant, and especially those in the first trimester of pregnancy, requires that the potential benefit be weighed against the possible hazard to mother and child. Use of the drug during lactation is not recommended. Mammalian reproductive and teratogenic studies with high multiples of the human dose have been negative.
Usage In Children Not recommended for use in children under 12 years of age.

Precautions
In patients with diabetes mellitus there may be alteration of insulin requirements due to dietary restrictions and weight loss. Pre-Sate (chlorphentermine hydrochloride) should be used with caution when obesity complicates the management of patients with mild to moderate cardiovascular disease or diabetes mellitus, and only when dietary restriction alone has been unsuccessful in achieving desired weight reduction. In prescribing this drug for obese patients in whom it is undesirable to introduce CNS stimulation or pressor effect, the physician should be alert to the individual who may be overly sensitive to this drug. Psychologic disturbances have been reported in patients who concomitantly receive an anorectic agent and a restrictive dietary regimen.

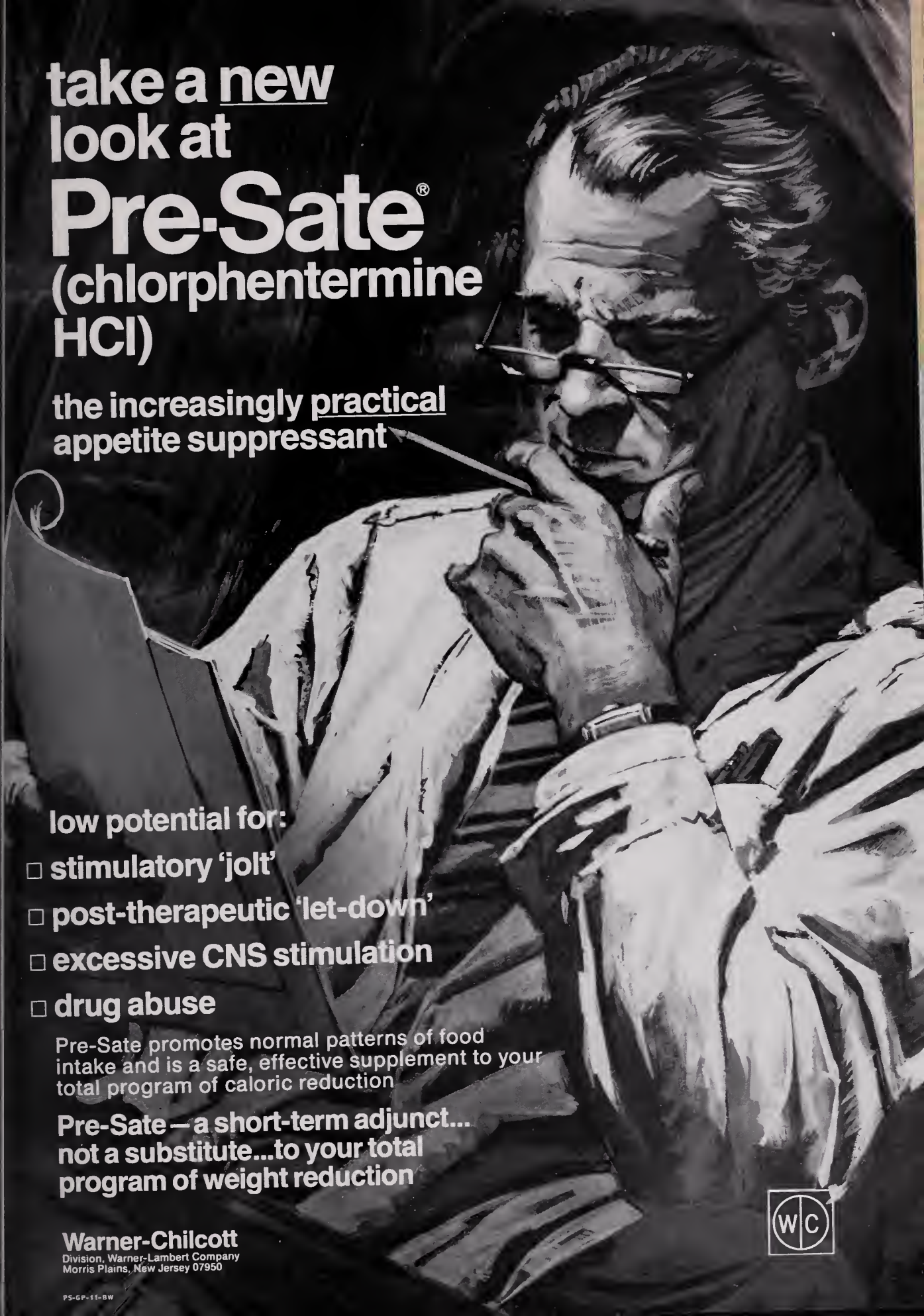
Adverse Reactions
Central Nervous System: When CNS side effects occur, they are most often manifested as drowsiness or sedation or overstimulation and restlessness. Insomnia, dizziness, headache, euphoria, dysphoria, and tremor may also occur. Psychotic episodes, although rare, have been noted even at recommended doses. **Cardiovascular:** tachycardia, palpitation, elevation of blood pressure. **Gastrointestinal:** nausea and vomiting, diarrhea, unpleasant taste, constipation. **Endocrine:** changes in libido, impotence. **Autonomic:** dryness of mouth, sweating, mydriasis. **Allergic:** urticaria. **Genitourinary:** diuresis and, rarely, difficulty in initiating micturition. **Others:** Paresthesias, sural spasms.

Dosage and Administration
The recommended adult daily dose of Pre-Sate (chlorphentermine hydrochloride) is one tablet (equivalent to 65 mg chlorphentermine base) taken after the first meal of the day. Use in children under 12 not recommended.

Overdosage
Manifestations: Restlessness, confusion, assaultiveness, hallucinations, panic states, and hyperpyrexia may be manifestations of acute intoxication with anorectic agents. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension, or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.
Management: Management of acute intoxication with sympathomimetic amines is largely symptomatic and supportive and often includes sedation with a barbiturate. If hypertension is marked, the use of a nitrate or rapidly acting alpha-receptor blocking agent should be considered. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

How Supplied
Each Pre-Sate (chlorphentermine hydrochloride) tablet contains the equivalent of 65 mg chlorphentermine base, bottles of 100 and 1000 tablets.

Full information is available on request.

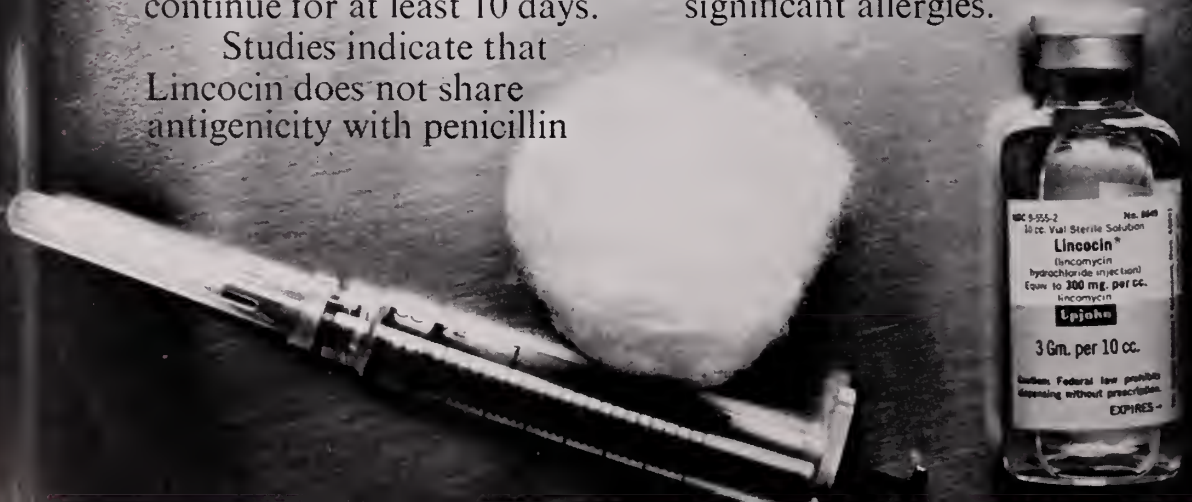

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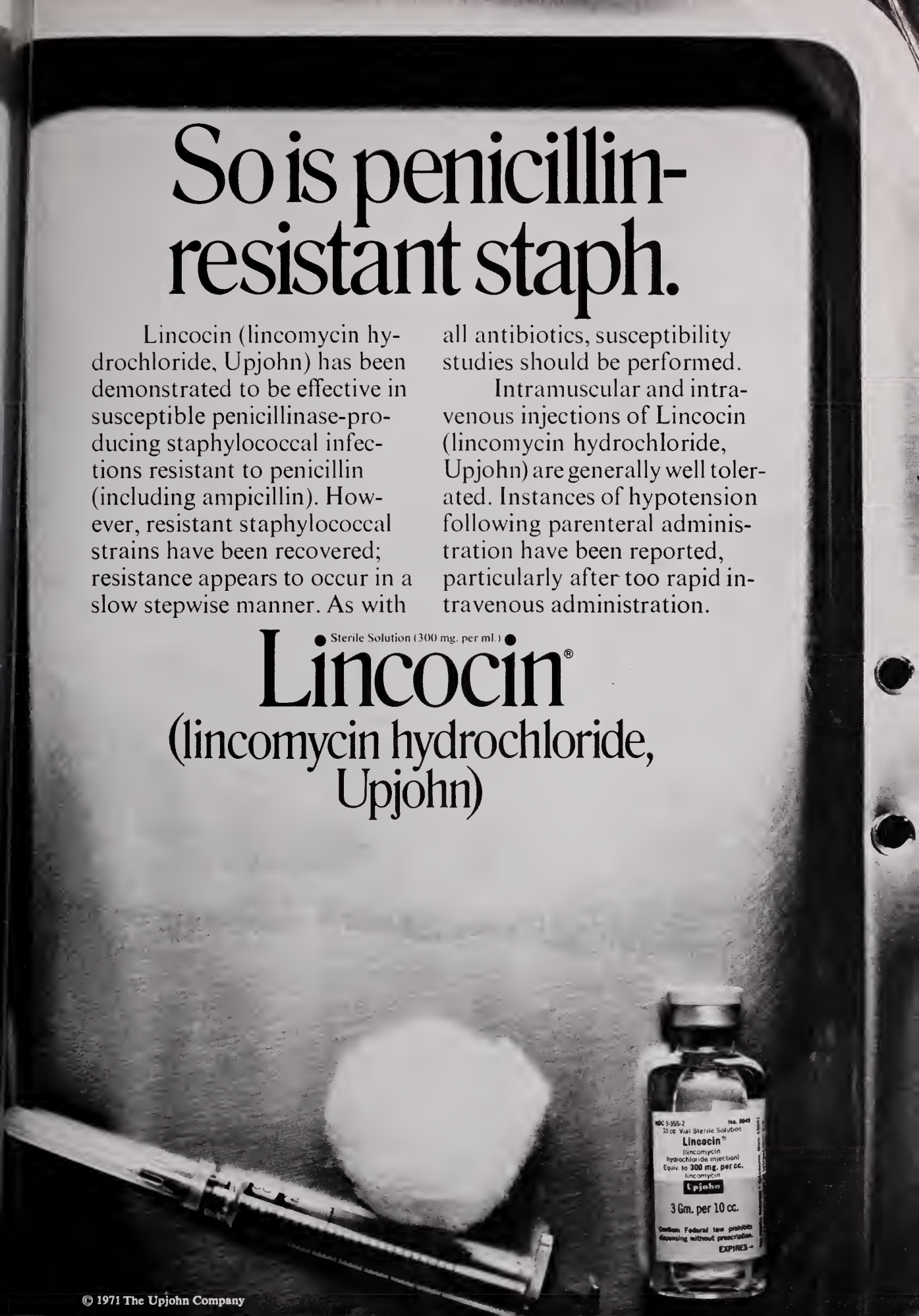
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Sterile Solution (300 mg. per ml.)

Lincocin®
(lincomycin hydrochloride, Upjohn)



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(lincomycin hydrochloride, Upjohn) for respiratory tract, skin, soft-tissue, and bone infections due to susceptible streptococci, pneumococci, and staphylococ

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WARNINGS: Cases of severe and persistent diarrhea have been reported and at times drug discontinuance has been necessary. This diarrhea has been occasionally associated with blood and mucus and at times has resulted in acute colitis. This reaction usually has been associated with oral therapy, but occasionally has been reported following parenteral therapy. Although cross sensitivity to other antibiotics has not been demonstrated, make careful inquiry concerning previous allergies or sensitivities to drugs. Safety for use in pregnancy has not been established and Lincocin is not indicated in the newborn. Reduce dose 25 to 30% in patients with severe impairment of renal function.

PRECAUTIONS: Like any drug, Lincocin should be used with caution in patients having a history of asthma or significant allergies. Overgrowth of nonsusceptible organisms, particularly yeasts, may occur and require appropriate measures. Patients with pre-existing monilial infections requiring Lincocin therapy should be given concomitant antimonilial treatment. During prolonged Lincocin therapy, periodic liver function studies and blood counts should be performed. Not recommended (inadequate data) in patients with pre-existing liver disease unless special clinical circumstances indicate. Continue treatment of β-hemolytic streptococci infection for ten days to diminish likelihood of rheumatic fever or glomerulonephritis.

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OCTOBER, 1971

Patients fell asleep quickly

Dalmane (flurazepam HCl) 30 mg reduced awake time—both before and after falling asleep - by fifty percent of pretreatment values in patients with insomnia.[1,2]

Two sleep laboratory studies recently confirmed findings of earlier studies of this type, namely, that Dalmane 30 mg was effective in patients who had trouble falling asleep, staying asleep or both. One 30-mg capsule of Dalmane usually induced sleep within 22 minutes, decreased the number of awakenings and the wake time after the onset of sleep, and provided 7 to 8 hours of sleep without need to repeat dosage during the night.

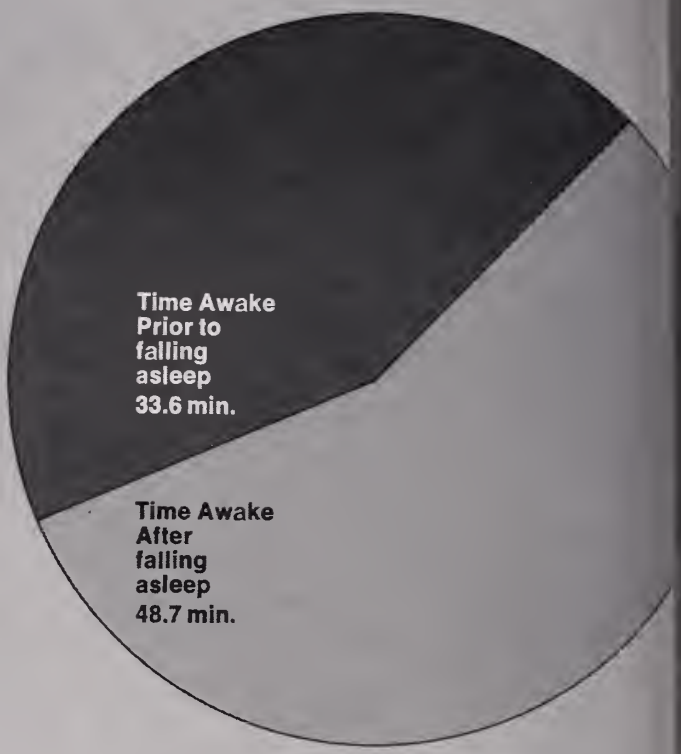
These studies utilized identical protocols and included eight insomniac patients. Sleep laboratory measurements in a limited number of patients are derived from all-night electro-encephalographic, electro-oculographic and electromyographic tracings. Unlike traditional methods of evaluation, they are quantitative, reproducible and projectable to large numbers of subjects.

Results shown represent average values in all subjects for the three consecutive nights of placebo administration prior to Dalmane therapy and the seven consecutive nights on Dalmane 30 mg.

Dalmane is also relatively safe, as reported in clinical studies. Instances of morning "hang-over" have been relatively infrequent; paradoxical reactions (excitement) and hypotension have been rare. Dizziness, drowsiness, lightheadedness and the like were the side effects noted most frequently, particularly in the elderly or debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

References: 1. Frost, J. D., Jr.: "A System for Automatically Analyzing Sleep," Scientific Exhibit presented at Clinical Convention, A.M.A., Boston, Nov. 29-Dec. 2, 1970, and Aerospace M.A., Houston, April 26-29, 1971.
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley, N.J.

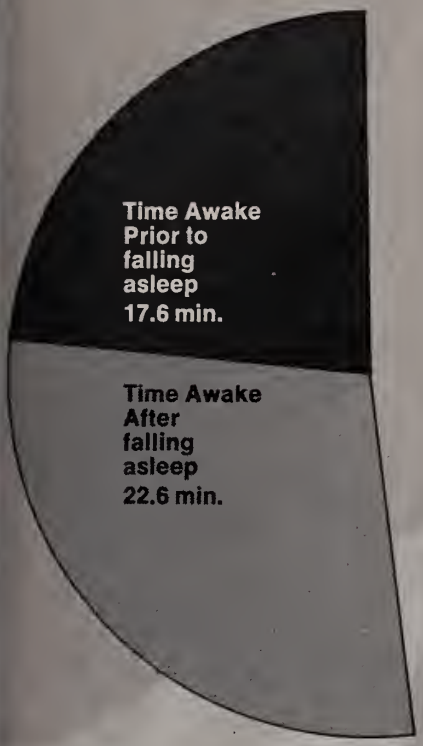
Before Dalmane (flurazepam HCl)



Measurements of sleep in the sleep laboratory are obtained with electroencephalographic, electro-oculographic and electromyographic recordings.

nd slept through the night

On
Dalmane
(flurazepam HCl)



rage sleep laboratory measurements in cited studies

ameter	Before Dalmane	On Dalmane
ıe required to fall asleep	33.6 min.	17.6 min.
ke time after onset of sleep	48.7 min.	22.6 min.
nber of wakeful periods after nset of sleep	12.2	8.4
al sleep time	420.0 min.	447.5 min.
al sleep percent	88.6	94.5

linical effectiveness as
roven in the sleep laboratory

Dalmane®
flurazepam HCl)

ıe 30-mg capsule h.s.—usual adult dosage.
ıe 15-mg capsule h.s.—initial dosage for
derly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

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President's Letter

Postgraduate Education

Because of the explosion of new knowledge in Medical Care, it becomes more necessary to develop programs of postgraduate education for our practicing physicians of the state. Many of our physicians in the state find it very difficult to spend periods of time away from their practice receiving postgraduate education. There are two programs in the state which I feel warrant our encouragement and support.

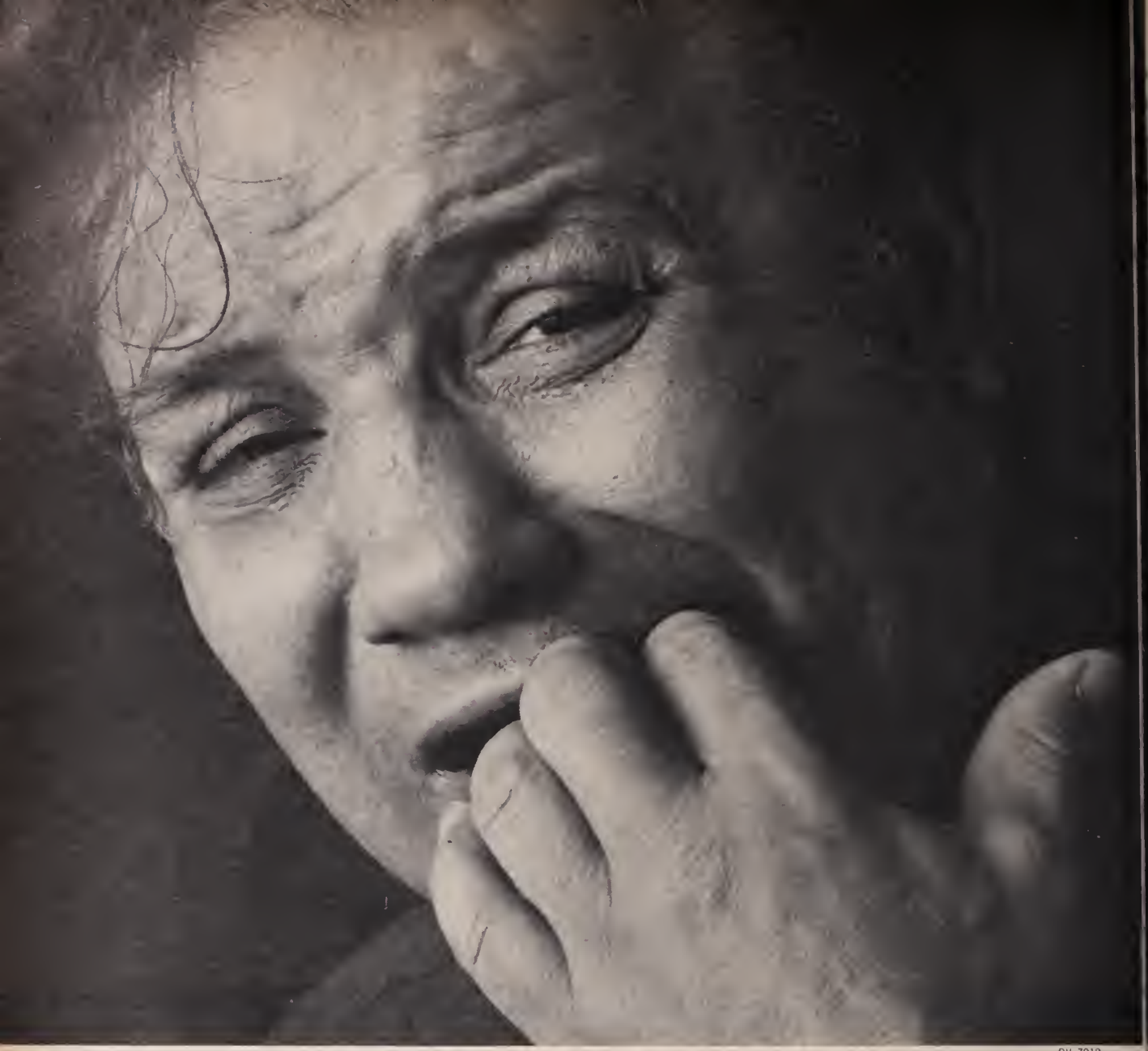
One program is carried out by hospital staffs who invited physicians in various specialties to spend an afternoon and evening with them about six times each year. This specialist sees patients in consultation with the practicing physician in the afternoon and then spends the entire evening discussing various problems within his specialty. In this way the practicing physician can be brought up-to-date on new developments within a given specialty while not leaving his community. Hibbing General Hospital has had a similar program for many years, which has been regarded as highly successful and very educational by the physicians in the area.

Another meritorious program is being proposed by the Postgraduate Medical Education at the University in conjunction with the Regional Medical Program. This program would establish one-to-three day refresher courses in varying specialties in nine areas in the state having state colleges. These courses would be offered at the State College and would be specially designed to interest the practicing physician in that given community. The refresher faculty would rotate throughout the nine areas so that each area would have a program approximately every one to two years. This would bring refresher courses closer to the practicing physician and make it much easier for him to attend these courses. The nine areas being considered at this time are Bemidji, Marshall, Mankato, Moorehead, St. Cloud, Winona, Duluth, Rochester and the Minneapolis campus. In order to make these programs successful and interesting to the area physicians, a committee would be formed to decide on a representational and meaningful curriculum.

I feel that both of the above programs are necessary in an effort to keep our practicing physicians up-to-date in medical treatment. The first program could be initiated by every major hospital staff in Minnesota and should have major emphasis on consultation and treatment. The Medical Refresher Course should have emphasis on new developments in medical care and spend some time introducing the physician to other means of education such as audio-visual material which could be at his immediate disposal. I would encourage physicians in the state to develop educational programs such as I have mentioned. I would also encourage you to support the Postgraduate Medical Education Program of one-to-three day refresher courses when they are developed in your region.

Robert T. Kelly

President
Minnesota State Medical Association



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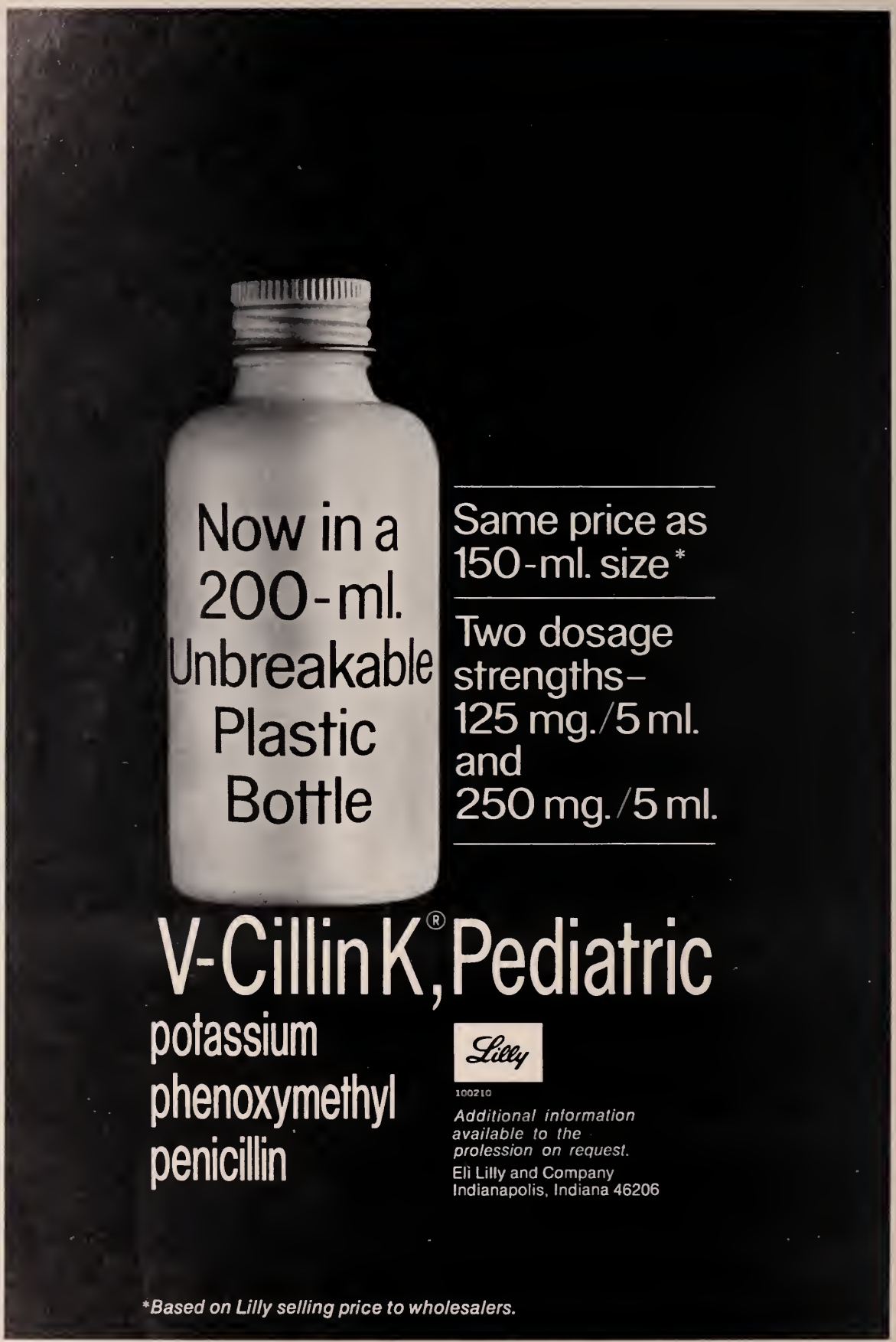
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Diagnostic Laparoscopy*

P. P. WILLIAMS, M.D.† AND R. P. BENDEL, M.D.†

IMPROVED INSTRUMENTATION and anesthetic techniques have resulted in a recent resurgence of interest in an endoscopic technique some 70 years old. With proper case selection and adherence to basic, proven precepts, laparoscopy can be a valuable addition to the gynecologist's diagnostic armamentarium.

Known variously as Kölioskopie, coelioskopee, peritoneoscopy, and laparoscopy, the technique has enjoyed an interesting and gradual development over the years. Steptoe[1] and Choen[2] have detailed well the historical and developmental aspects of laparoscopy.‡

‡1902: Kelling of Dresden publishes a report of experimental laparoscopy on a dog performed in 1901.
1910: Jacobaeus of Stockholm describes the first use of the procedure on a human.
1910-20: Numerous reports appear, in the European literature, of the technique and its variants.
1920: A report by Orndorff of Chicago, a radiologist, of the first use of the technique in the United States.
1934: Ruddock's report of two hundred cases stimulates interest in the United States. This report discussed the use of ancillary instrumentation.
1940's: Techniques of culdoscopy develop and supercede interest in laparoscopy except in isolated pockets in Europe.
1950's: Interest abroad increases with the development of refined instrumentation, the introduction of fiberoptics, and the perfection of techniques of still and motion picture photography.
1960's: The technique and its potentials become popular in Great Britain and finally here in the United States.
1970's: Ever widening interest is occasioned in the technique and more centers, academic and non-academic, are becoming equipped to perform laparoscopy.
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Instrumentation

The Scope

Several types of laparoscopes and the necessary ancillary equipment are available. The modern laparoscope consists of a lens system, a means of illumination, and the rigid tubular housing, in diameters from 4 to 10 millimeters with 180° direct or 135° fore-oblique lens systems. The scope of today relies on fiber-optic ("cold light") illumination. Older instruments used a potentially more dangerous incandescent bulb. Photography necessitates a more powerful light. Appropriate light sources are available from the manufacturers. Introduction of the laparoscope into the peritoneal cavity requires a special trochar and valved cannula. The tip of the trochar may be either conical or pyramidal, with the latter providing greater ease of penetration through the abdominal wall.

Carbon Dioxide Source

Other basic equipment includes a pneumoperitoneum needle and a carbon dioxide source with appropriate pressure-flow reduction and monitoring systems. The necessary vaginal instruments are readily available.

Ancillary equipment useful in realizing the full potential of the procedure in diagnosis includes measuring and manipulating probes, forceps, and camera and lens systems.

Technique

The patient is prepared as for any major abdominal procedure. Under general endotracheal anesthesia, she is placed in semi-lithotomy position and prepared appropriately.

Cannulating the Cervix

Following catheterization of the bladder, the cervix is exposed, a tenaculum affixed, and a standard Jarcho cannula inserted into the cervix and articulated with the tenaculum. A self-retaining patency cannula may also be used.

Inserting Pneumoperitoneum Needle

While this is being accomplished, a second member of the team introduces the pneumoperitoneum needle into the abdominal cavity at the inferior border of the umbilicus by a twisting Z-tract method which prevents leakage when the carbon dioxide is instilled. A saline-filled syringe is attached to the needle to test position. The easy injection of the saline or the return of air bubbles on aspiration usually indicates satisfactory peritoneal penetration.

Carbon Dioxide Introduction

Tubing from the carbon dioxide source is connected and, with the patient in 20 to 30 degree

*Presented, in part, April 25, 1970 at the semi-annual meeting of the Minnesota Obstetrical and Gynecologic Society, Rochester, Minnesota.

†Department of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis, Minnesota.

Trendelenberg position, two to three liters of carbon dioxide are introduced to a pressure of 30 to 50 centimeters of water. Failure of the abdomen to distend or the appearance of subcutaneous emphysema indicates malposition of the needle.

Introducing the Cannula and Scope

When a satisfactory degree of distention has been produced, the needle is withdrawn, a one-centimeter incision is made at the inferior border of the umbilicus, and the trochar cannula is introduced. The trochar is then withdrawn and, after preliminary warming, the laparoscope is introduced. The scope and cannula may be freely moved about and, if desired, in a 360° circle for complete visualization.

Viewing the Structures

Manipulation of the vaginal instruments enhances the view of the pelvic structures. If further manipulation is required the abdominal wall is transilluminated in either lower quadrant to delineate blood vessels and a second, smaller trochar-cannula is introduced under direct vision. This second cannula will accept graduated probes, forceps, and, if desired, instruments for operative laparoscopy. In selected cases, tubal patency may be demonstrated by injection of dye such as indigo-carmine through the hysterogram cannula with visualization of intraperitoneal spill. At any point following insertion of the laparoscope, a special lens may be attached to the eye-piece and, using proper illumination, still or motion picture photography accomplished.

As alluded to, operative procedures, such as biopsies, cautery, *adhesionolysis,* sterilization, and, as recently reported, removal of a translocated intrauterine device may be accomplished.

When the examination has been completed, the pneumoperitoneum is evacuated as completely as possible, and the skin wounds sutured or closed with wound clips. If findings indicate, it is entirely feasible to proceed immediately with laparotomy under the same anesthetic. A dilatation and curettage may be performed before the patient leaves the operating room. Unless a laparotomy has been performed, the patient can be discharged from the hospital the following day with minimal postoperative discomfort.

Indications

It has been said that laparotomy represents the ultimate diagnostic procedure. It can be more easily said that laparoscopy is the ultimate diagnostic procedure short of laparotomy.

In the patient with *a suspected, but unruptured tubal pregnancy* or doubtful *tubal abortion,* the laparoscope can provide an answer.

In the investigation of the infertile patient, proper utilization of ancillary instruments will allow visualization of the entire pelvis. Tubal and peritubal pathology can be easily noted. *Evidence of ovulation* can be documented. Tubal patency can be confirmed or refuted with dye studies. Maximal information can be obtained with relatively little expenditure of time and effort.

Laparoscopy lends itself well to the investigation of *both primary and secondary amenorrhea.*

The patient with persistent, *unexplained pelvic pain* is often a candidate for laparoscopy. Even a negative examination, perhaps supported by pictures, can be of therapeutic value.

Confirmation or refutation of suspected *pelvic endometriosis* and assessment of chronic *pelvic inflammatory disease and its response to therapy* are amenable to laparoscopy.

A definitive diagnosis regarding *small uterine or ovarian masses,* including those complicating the first three months of pregnancy, can result from laparoscopic examination.

The technique may be used profitably in the diagnosis of *some causes of ascites* and in the evaluation of certain *pelvic malignancies and particularly their response to therapy.*

Contraindications

Just as there are indications for laparoscopy *contraindications* exist. Laparoscopy is contraindicated in those patients with such *respiratory or circulatory embarrassment* that positioning or the required pneumoperitoneum would produce added hazard. It is absolutely contraindicated in the face of *advanced malignancy.* It is also contraindicated in *diaphragmatic hernia* or *abdominal, umbilical,* or *crural herniation* where herniation of viscera or adhesions may present hazards. Careful consideration should be given before attempting the procedure in the presence of *acute peritonitis.*

Complications

Any procedure is fraught with potential or real hazards or complications. Laparoscopy is no exception. Reported[3] complications include:

1. Puncture of vessels:
   a. Anterior abdominal wall
   b. Intra-abdominal
2. Perforation of an intra-abdominal viscus
3. Parietal emphysema
4. Cardio-respiratory embarrassment
5. Effect of high-pressure gas injection:
   a. Gas embolism
   b. Mediastinal emphysema and pneumothorax
   c. Rupture of diaphragm
   d. Aggravation of existing hernias

Two deaths have been reported[4] during laparoscopy. One appears to have been related to retroperitoneal carbon dioxide and pneumothorax. Details of the second case are vague. Our experience, to date, has been devoid of major complications.

Experience

Tables 1 through 5 and Figures 1 through 6 itemize our studies of 141 cases.



Fig. 1—Normal pelvis. The uterus is elevated. Note the taut uterosacral ligaments and the pool of dye demonstrating tubal patency.

TABLE 1

Indication	Number of Cases
Pelvic mass	10
Pelvic pain	32
Primary or secondary amenorrhea	5
Primary or secondary infertility	52
Miscellaneous	5



Fig. 2—Indigo carmine dropping from the fimbrial end of a normal, patent tube.

TABLE 2

Age Range	Number of Cases
13-29	7
20-29	65
30-39	25
40-	7

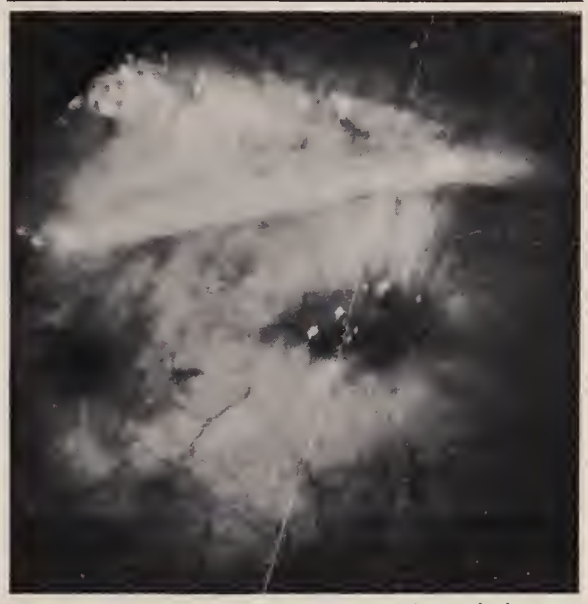


Fig. 3—"Powder burn" lesions of endometriosis. Such minimal disease is easily seen through the laparoscope.

TABLE 3

Findings—Infertility	Number of Cases
Normal pelvis	25
Pelvic adhesions	14
Endometriosis	10
Sclerocystic ovaries	2
Developmental anomaly	1



Fig. 4—Pelvic adhesions.

TABLE 4

Findings	Number of Cases
Normal pelvis	14
Adhesions	7
Endometriosis	6
Pelvic inflammatory dis.	2
Myomatous uterus	1
Ectopic pregnancy	1
Tubal torsion	1



Fig. 5—Small, cauliflower-like implants of metastatic carcinoma are seen studding serosal surfaces.

TABLE 5

Findings	Number of Cases
Normal pelvis	2
Corpus luteum cyst	2
Endometriosis	2
Bilateral ovarian fibromatosis	1
Ectopic pregnancy	1
Recurrent dysgerminoma	1
Intraligamentous myoma	1



Fig. 6—The enlarged white ovaries of a patient with sclerocystic ovary disease are readily appreciated. Again, the uterus is elevated.

Discussion and Commentary

The instrumentation and technique presented here are rather standard and are identical with or similar to those mentioned by others.[1,2]

The site of the initial puncture may be modified depending on circumstances. The presence of a scar from a prior laparotomy may dictate a lateral umbilical, a para-umbilical, or a pararectus abdomis approach at the level of the umbilicus in an attempt to avoid possible adhesions. Lower quadrant sites have been suggested, but cannot be recommended.

Details of operative laparoscopy are beyond the scope of this paper. Techniques of fulguration, biopsy, and sterilization have been worked out and additional techniques are being developed. This aspect of laparoscopy will be the subject of a forthcoming publication.

Fortunately, major reported complications are few. The majority are associated with creation

of the pneumoperitoneum, and extra care must be exercised in considering this step. In addition to those complications mentioned, cardiac irregularities have been reported.[6] Alterations in blood gases do occur with the creation of the pneumoperitoneum. These have been documented but do not appear to be significant.[7,8]

The experience at the University of Minnesota Hospitals mirrors that of other centers. The largest number of patients fell in the 20-29 year-old group. This undoubtedly reflects the use we have made of the laparoscope in the investigation of infertility. In this application, the technique lends itself well for its direct return of information. Use in the evaluation of pelvic pain circumvented laparotomy in several cases. The proportionately high number of negative examinations would be expected by the nature of the patient population presenting with this complaint. The numbers falling into the other groups demonstrate what might be expected but are, as yet, too small for inference or conclusion.

Conclusion

Implementation of this revitalized 70-year-old technique at University of Minnesota Hospitals has proved satisfactory. We have found it simple to perform, productive of valuable information, and devoid of major complications. We feel the procedure has merit; we recommend it to others; we intend to continue and expand its utilization at our institution.

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Doctor Darwin's Ingenuity

Mrs. Clark had her under-eyelid so turned in that the hairs were constantly covered by the eyeball. The eye had been kept thus in a painful and inflamed state for several months. I applied a slip of sticking plaster from the upper part of the ala of the nose to the temple, and put under it a hard compress about the size of a pea, which kept the cilia turned outwards in its natural place; and in a fortnight it kept there spontaneously, and became quite well. This gave me much satisfaction, as I had seen Chev. Taylor fail in effecting this by a cruel operation of cutting a piece of skin between the eyelid and the external prominent part of the cheek-bone, and drawing together the lips of the wound with a needle and thread.*

*Erasmus Darwin as quoted in Hesketh Pearson: Doctor Darwin, 1930.

At the Mayo Clinic in Minnesota you are bound to hear about the time a bustling woman stopped Dr. Will Mayo and asked, "Are you the head doctor here?"

"No, Madam," replied Dr. Will. "My brother is the head doctor. I'm the belly doctor."*

*Modern Handbook of Humor, Ralph Woods, Editor.

Man cannot create the current events, he can only float with them and steer. —Bismarck, Chancellor of Prussia, 1870.

Oral Surgery

Cloxacillin for Prophylaxis

WILLIAM JOSEPH MARTIN, M.D.*, DANIEL E. WAITE, D.D.S.‡,
JOHN J. MILLER, JR., D.D.S.‡, AND ALEXANDER SCHIRGER, M.D.†

TRANSIENT BACTEREMIA is often the sequela of oral surgical procedures. The effectiveness of several antibiotics in the prevention of bacteremia has been reported previously.[1-5] The purpose of this study was to evaluate the effectiveness of cloxacillin in preventing preoperative and postoperative bacteremias.

Materials and Methods

Data on patients undergoing typical oral surgical procedures form the basis of this study. The procedures varied from simple, uncomplicated extractions and alveolectomies to extractions of abscessed teeth and impacted third molars, with and without pericoronitis.

Cloxacillin, a biosynthetic penicillin, is effective against penicillin-sensitive, gram-positive organisms and the penicillinase-producing staphylococci. It is well absorbed from the gastrointestinal tract and is resistant to destruction by gastric acid.

Cloxacillin in capsule form was administered in four 500-mg doses at six-hour intervals, beginning 18 hours before operation and ending just prior to surgery. Both aerobic and anaerobic blood samples were obtained for culture immediately prior to surgery and again 24 hours later. A total of 27 patients participated, after careful screening to eliminate those with penicillin allergy, medical contraindications, or concomitant therapy with other antibiotics.

The samples were collected under aseptic conditions by the use of sterile, prepackaged, intravenous polyethylene tubing with appropriate needles at either end and sterile glass vacuum bottles. The samples were incubated for five days, and any growth was cultured.

Results (Table)

Only one of the samples yielded a postive culture (postoperative coagulase-positive staphylococci), even though several abscessed teeth and third molars with pericoronitis had been removed. The one positive culture may have occurred because the patient failed to take the prescribed dosage according to schedule. The organism was susceptible to oxacillin in vitro, but was not tested for cloxacillin susceptibility.

TABLE
Result of Blood Culture with Use of Cloxacillin For Prophylaxis Prior to Oral Surgery

	Negative		Positive	
Time	Aerobic	Anaerobic	Aerobic	Anaerobic
Immediately preop.	27	27	0	0
24 hours postop.	27	26	0	1

Conclusion

In this study, cloxacillin has demonstrated its capability of eliminating or preventing preoperative and postoperative bacteremias. However, because of its particular value in treating bacteremias caused by penicillinase-producing staphylococci, and because other antibiotics have proved to be effective when employed in a prophylactic regimen, cloxacillin probably should be reserved for patients with resistant staphylococcal infections. A history of penicillin allergy would preclude the use of cloxacillin. Patients susceptible to subacute bacterial endocarditis who are given the drug should be followed closely after surgery.

*Mayo Clinic and Mayo Foundation: Division of Infectious Diseases and Internal Medicine.
†Division of Cardiovascular Diseases and Internal Medicine.
‡University of Minnesota: School of Dentistry.
Dr. Martin died May 19, 1970.

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Behind an able man there are always other able men.—Chinese Proverb

Anaphylactic Reaction after Sodium Dehydrocholate (Decholin) Use

GUSTAVUS A. PETERS, M.D.* AND DAVID M. WITTEN, M.D.†

ANAPHYLACTIC REACTIONS to sodium dehydrocholate (Decholin) have been infrequent. Recently, Patton[1] has reviewed the literature and noted 22 previously reported cases of reactions to Decholin. He added five more, of which two involved vascular collapse and one a positive skin reaction to Decholin. Elliott, Vidrine, and Goldman[2] reviewed the American literature and noted that Norman,[3] and Coggins, Skinner, and Burrell[4] both had reported one case each of circulatory collapse or anaphylactoid reaction. These two cases with the two cases of Patton and our case make five cases of anaphylactoid reactions. Elliott et al. further commented on the rarity of allergic reactions. Leys[5] was the first to call attention to the potential toxicity and lethality of Decholin.

Decholin has been used since 1931 when Winternitz and associates[6] introduced it for the study of circulation time. However, the practical usefulness of this agent has been questioned by Selzer, Dunlap, Wray, and Russell,[7] who stated that its usefulness probably is limited to the diagnosis of high output cardiac states.

Although Decholin is the least toxic of the bile salts, Horrall[8] noted that a 2% solution of dehydrocholic acid stopped the heart in a few seconds. In 1939, Wakim, Essex, and Mann[9] pointed out the toxic effects of bile salts on the perfused and isolated rabbit heart by producing vagotonia, arrhythmia, bradycardia, ventricular extrasystoles, blocks of different degrees, ventricular fibrillation, and cardiac arrest.

The patient to be reported on was an asthmatic in whom acute laryngeal edema with moderate associated bronchospasm developed, which required emergency supportive measures for relief. However, a few days later she died of congestive heart failure after nephrectomy for a large renal mass that proved to be a hydronephrotic duplication of the upper segment of the left kidney. The congestive heart failure probably was due to severe coronary atherosclerosis and mitral valvular insufficiency complicated by adrenal insufficiency.

*Mayo Clinic and Mayo Foundation: Division of Allergic Diseases and Internal Medicine.
†Department of Diagnostic Roentgenology.

Case Report

A 67-year-old white woman was hospitalized on November 24, 1967. She had a 16-year history of hypertension, but the hypertension was not severe enough to necessitate drug therapy. She had a history of an enlarged heart and cardiac murmur but none of rheumatic fever. For six years she had been receiving digitoxin because of the heart condition and methylprednisolone because of asthma. Her asthma had begun in 1955 and was associated with an allergy to corn products. Avoidance of these controlled the asthma, although she had to have the support of methylprednisolone, a half tablet twice a day. The use of this steroid was discontinued five days prior to her admission. She had been hospitalized at another institution on October 29, 1967, because of acute dyspnea. During the course of that hospitaliziation, she was given an excretory urogram, which revealed a sizable mass in the upper part of the left kidney. Because of the existing hypertension and the mass, a pheochromocytoma was suspected and she was referred to the Mayo Clinic.

On the day of admission on November 24, 1967, her blood pressure was 150/80 mm Hg. The pulse rate and temperature were normal. She had xanthelasma around both eyes. Her chest was clear on auscultation. She had a grade 3 apical systolic murmur extending into the left axilla. The jugular venous pressure was normal, and there was no hepatomegaly or pedal edema. Excretory urography revealed a mass in the upper pole of the left kidney.

Two days later (on November 26) intravenous nephrotomography was requested. Prior to the procedure, she was given 100 mg of Decholin intravenously to assess circulation time. Immediately she experienced acute bronchospasm, which required endotracheal intubation and 0.3 ml of 1:1000 epinephrine subcutaneously plus 250 mg of aminophyllin intravenously and 100 mg of hydrocortisone. She responded well to this therapy but was hospitalized three days in the intensive care unit. The following day (on November 27) she was asymptomatic.

It was decided to proceed with the surgical exploration of the left renal mass. On November 27, the patient was given 100 mg of cortisone acetate in two doses, and on November 28, she received 200 mg of the drug, plus prednisone orally, until the time of the operation.

Left nephrectomy and partial ureterectomy were performed on November 30. Duplication of the pelvis and ureter was found within the left renal mass, as well as a nonfunctioning hydronephrotic upper segment of the kidney. She had no trouble from the anesthetic and did well for two days after the operation. However, she had an acute asthmatic attack and subsequently developed congestive failure and died on December 3. She did not receive steroids after the operation.

Prior to her death, laboratory study showed a hemoglobin value of 10.9 gm/100 ml, a sulfobromophthalein retention of 12%, and a cholesterol level of 288 mg/100 ml. A roentgenogram of the chest showed calcification of the aorta. An electrocardiogram taken on November 27 showed left ventricular hypertrophy, and one taken the following day showed slight ST depression, suggestive of myocardial ischemia. Astrup studies of December 2 revealed a pH of 7.42, a pCO_2 of 34 to 42 mm Hg, a standard bicarbonate value of 22.5 mEq/liter, a base deficit of 1.9 mEq/liter, and a buffer base of 45.7 mEq/liter. The following day the Astrup test was repeated shortly before the patient's death and showed a pH of 7.36, a pCO_2 of 21 to 28 mm Hg, a standard bicarbonate level of 15 mEq/liter, a base deficit of 12.4 mEq/liter, and a buffer base of 34.7 mEq/liter. The sodium level was 135 mEq/liter, potassium level 4.5 mEq/liter, CO_2 combining power 10.3 mEq/liter, and chloride level 101 mEq/liter shortly before her death. A skin test to Decholin was not done.

Autopsy revealed that the patient died primarily of coronary arterial disease; coronary atherosclerosis of grade 3 to 4 was found, as well as a mitral valvular deformity, with clinical evidence of valvular insufficiency. There was evidence of the previous left nephrectomy and a fibrotic stricture of the distal segment of the left ureter. The heart was enlarged (425 gm; normal 270 gm). There was evidence of acute pulmonary edema with early bronchopneumonia (right, 735 gm, left 445 gm) and pleural effusion (1,000 ml on each side). Acute passive congestion with centrilobular necrosis was noted in the liver. There was arterial nephrosclerosis with small scars and atheromatous embolism of both kidneys. Also noted were adrenal cortical atrophy, uterine myomatas, and two cystic infarcts in the right caudate nucleus. There was atherosclerosis of grade 4 in the aorta and of grade 2 in the cerebral arteries, as well as atheromatous embolism of the pancreas and kidneys. Bone-marrow embolism of the lungs was seen; this probably resulted from attempted resuscitation.

Discussion

In 1944 Leys[5] reported three patients with reactions to Decholin, one of whom died. He believed that Decholin should not be used because of its possible lethal consequences. Winternitz[10] noted three reactions of nonfatal collapse in 2,000 injections and believed that this was about the incidence one should expect with speed injection of any anisotonic and anisosmotic solutions, particularly in patients with terminal heart failure. He admitted that he had almost abandoned the method in favor of the calcium method, which involved 5 ml of a 20% solution of calcium gluconate or 10% solution of calcium chlorate. In our experience with more than 4,000 patients in whom Decholin had been used for circulation-time assessment as part of intravenous nephrography, the patient described herein is the only one in whom a reaction developed.[11]

Conclusion

Although Decholin has been used for many years in the measurement of the circulation time, the clinical value of this test is limited, and the drug carries with it a small but definite hazard of reaction. The incidence of reactions to intravenously administered Decholin is low, but the potential for severe or even fatal reactions exists. The use of this material for determining circulation time should be limited to a few specific indications. If Decholin is used one should be prepared to combat any sudden reaction by having available for immediate use appropriate emergency drugs and equipment for vascular collapse. Our case tends to support the view of others that Decholin should be used with care in patients who have borderline cardiac compensation and in those who have a history of asthma; however, serious reactions have been reported in patients without any previous history of allergy.

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Fellows who roll up their sleeves seldom lose their shirts.—Mark Wachs

An Unusual Clivus Meningioma

JOSEPH WESTERMEYER, M.D., M.A.,* DAVID DANOFF, M.D.* and
MILTON ALTER, M.D., Ph.D.†

Castellano and Ruggiero[1] first suggested the term "clivus" meningioma for tumors such as the one discussed here; their series of 71 meningiomas of the posterior fossa includes nine cases with a well-described clivus meningioma. The patients ranged in age from 39 to 60 years; five were male and four, female. Symptoms ranged in duration from four months to five years; the median was one year. Seven died at surgery or within a few days afterward. The remaining two were worse after surgery.

Tristan and Hodes[2] presented 59 posterior fossa meningiomas, two of which originated on the clivus. They provided little clinical data.

Cushing and Eisenhardt[3] did not use the clivus meningioma category in their monograph on 313 patients with meningioma, but grouped them with tumors of the basilar groove. Hence the frequency of clivus meningiomas cannot easily be derived from their series.

DiChiro and Anderson,[4] in an extensive radiologic study of the clivus, reviewed the radiologic findings in six cases of clivus meningioma; their series did not include clinical data. Complete clinical reports on two patients with clivus meningioma, a 48-year-old female and a 61-year-old male were presented by Petit-Tutaillis and Daum.[5] The woman's symptoms had been present for three years. Following a vigorous course of radiotherapy, a craniectomy was performed. She died two months later. The man's symptoms had been present 15 months; he died the day after surgery.

The four patients with clivus meningioma described by Dany et al.[6] include three females and one male. One of these patients was a 23-year-old woman who died 50 days after surgery; the duration of her symptoms was not recorded. The other three patients ranged in age from 38 to 47 years; their symptoms had been present seven months to two years. Following surgery the two women died at two days and seven days respectively. The man, who had radiotherapy after subtotal removal, was alive and working 14 months after surgery.

Case Report

History

A 29 year-old truck driver was admitted to the Neurology Service at the Minneapolis Veteran's Hospital in 1968. In 1951 he had developed paralysis of the left vocal cord (cranial nerve X) following an illness diagnosed as viral bronchopneumonia. In 1957 he first noted ringing of the left ear (cranial nerve VIII). A myringotomy was performed, but the tinnitus persisted, and hearing on the left side was gradually lost. In 1960 he began to have double vision when looking to his left. Examination at that time demonstrated weakness of the lateral rectus muscle on the left (cranial nerve VI). The following year, pneumoencephalography and angiography were done but failed to show any abnormality. A left mastoidectomy was performed. In 1965 the patient developed difficulty with swallowing (cranial nerve X). A tonsillectomy was done, and an unsuccessful surgical attempt was made to correct the weakness of the left lateral rectus muscle. In 1968 he gradually developed numbness of the left side of his face (cranial nerve V) and difficulty with balance (?cerebellum).

Physical Examination

Upon admission, our patient was found to be alert, ambulatory and in no acute distress. Vital signs were normal. Hypalgesia was noted over the middle third and lower third of the left side of the face; the corneal reflex and nostril sensitivity on the left were decreased (cranial nerve V). The left eye deviated medially, and the patient could not move it laterally (cranial nerve VI). Facial muscles and taste on the left were impaired (cranial nerve VII). Hearing acuity of the left ear was markedly reduced. (cranial nerve VIII) The soft palate was paretic, and the left gag reflex was decreased (cranial nerve IX). The patient had difficulty swallowing, and he spoke in a raspy whisper (cranial nerve X). The left trapezius muscle was weak (cranial nerve XI). Marked atrophy was noted on the left side of the tongue (cranial nerve XII). Cerebellar dysfunction could not be elicited; deep tendon reflexes were normal.

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Fig. 1a—Selective left vertebral arteriogram demonstrates dorsal displacement of the intracranial position of the left vertebral artery off the clivus (double arrow). Note also downward displacement of tonsillar branch of posterior inferior cerebellar artery (single arrow), indicating tonsillar herniation.



Fig. 1b—Venous phase, left vertebral arteriogram, AP projection. Note left cerebellopontine angle mass with tumor stain (arrows) and dilated draining veins on surface of tumor.

Laboratory Procedures

The spinal fluid protein was 108 mg. percent; four lymphocytes were seen. Skull x-rays, x-rays of the internal auditory meatus, special views of the petrous ridges and a brain scan were normal. A posterior fossa angiogram demonstrated dorsal displacement of the left vertebral artery off the clivus (Figure 1A) and a tumor mass in the cerebellopontine angle region with a tumor stain (Figure 1B). A pneumoencephalogram was terminated because early films showed tonsillar herniation. On a Pantopaque clivogram, the left cerebellopontine cistern did not fill. The subarachnoid space over the odontoid process and the upper portion of C-2 vertebra did not fill; the right side of the clivus appeared normal.

Operative Findings

A suboccipital craniectomy revealed herniation of the tonsils and a kinking of the brain stem resembling an Arnold-Chiari malformation. Ragged tissue noted at the left latero-inferior wall of the posterior fossa led to a globular mass arising from the left clivus (Figure 2). Twenty-seven grams of tumor tissue were removed and the *osseous base at the medial edge of the jugular foramen* was cauterized. It was estimated that the tumor had been 95 percent removed prior to cautery. Exploration of the right cerebellopontine angle was negative. Pathological diagnosis was "mixed meningioma exhibiting fibroblastic, meningotheliomatous and psammoma elements" (Figure 3).

Clinical Course

Although the patient awakened promptly after surgery,

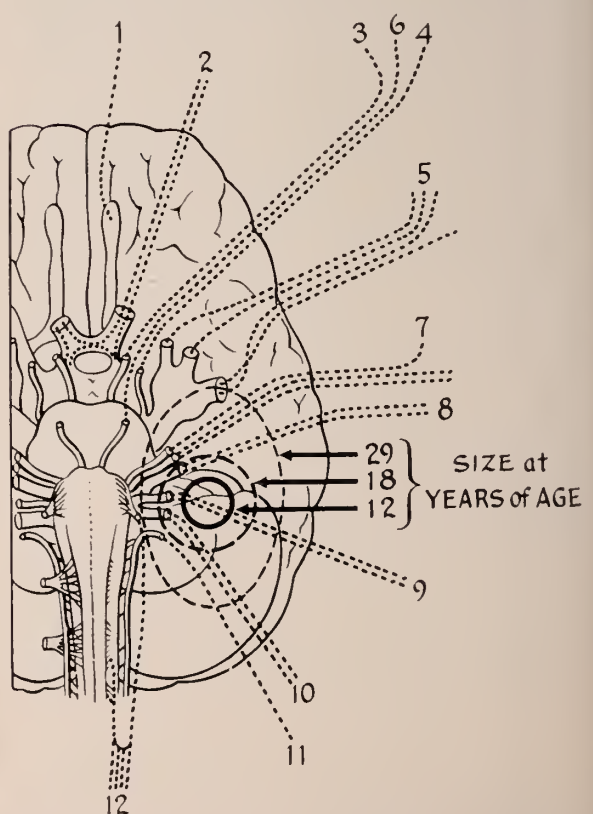


Fig. 2—Growth of clivus meningioma over period of years.

he had considerable difficulty speaking and swallowing. The next day he had a respiratory arrest. Tracheostomy was immediately performed and positive pressure breathing applied; shortly after, he began to breathe spontaneously. Post-surgical examination demonstrated intact motor function of the left fifth cranial nerve, but the left facial paresis (motor portion, cranial nerve V) was worse. The other cranial nerves were unchanged. Postoperatively the patient could swallow only small amounts of fluid and had to be maintained on nasogastric feedings; subsequently, a feeding gastrostomy was performed. There was gross incoordination of the left arm and leg. At 10 months after surgery, he was still improving. He could swallow and no longer required a gastrostomy. He walked without assistance, but his gait was still clumsy. The cranial nerve findings were unchanged, and a facial sling operation was carried out for cosmetic reasons (Figure 4).

Discussion

In this report we describe a patient with a clivus meningioma who has several unusual characteristics. He is the youngest male to present with such a tumor, and his duration of symptoms is the longest yet reported. More cranial nerves were involved (cranial nerves V through XII) than have been reported in the world's literature. Our patient is one of the few to survive virtually complete surgical removal of the tumor.

Characteristically, patients with a clivus meningioma have progressive unilateral involvement of the fifth through twelfth cranial nerves. Mild signs of intracranial pressure or cerebellar involvement may be present, but patients usually remain able to walk. Examination often demonstrates papilledema, homolateral reduced hearing, or reduced corneal reflex.

The most useful diagnostic test is posterior fossa angiography, which may demonstrate a posterior displacement of the basilar artery away from the clivus. Pneumoencephalogram may show posterior displacement of the aqueduct and fourth ventricle but often is inconclusive. Plain skull films are not usually helpful as clivus meningiomas do not produce remarkable signs of increased pressure; hyperostosis of the clivus and dorsum has been observed in one case. DiChiro and Anderson[4] recommend tomograms to demonstrate increased density of the surface of the clivus which contrasts with underlying normally cancellous bone. This suggestive finding was present in five of their six cases.

Most previous investigators (excepting Dany *et al.*) agree that clivus meningiomas should be considered inoperable since, in most hands, sur-

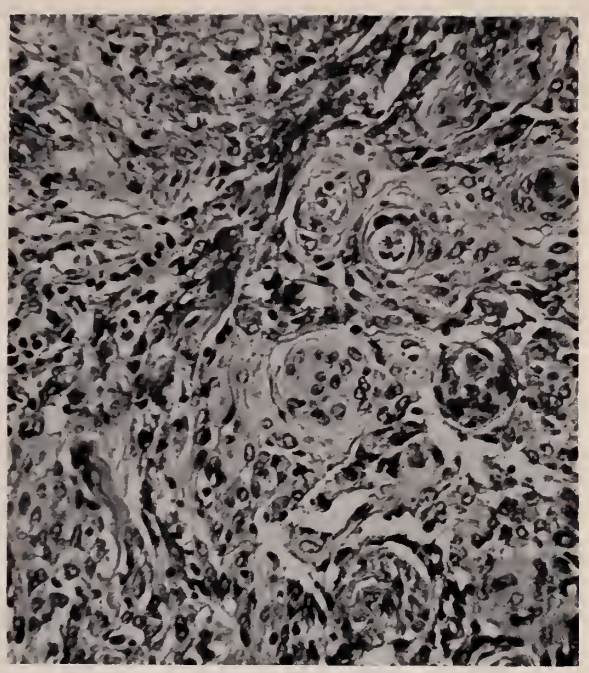


Fig. 3—This illustrates the characteristic histology of a meningioma.

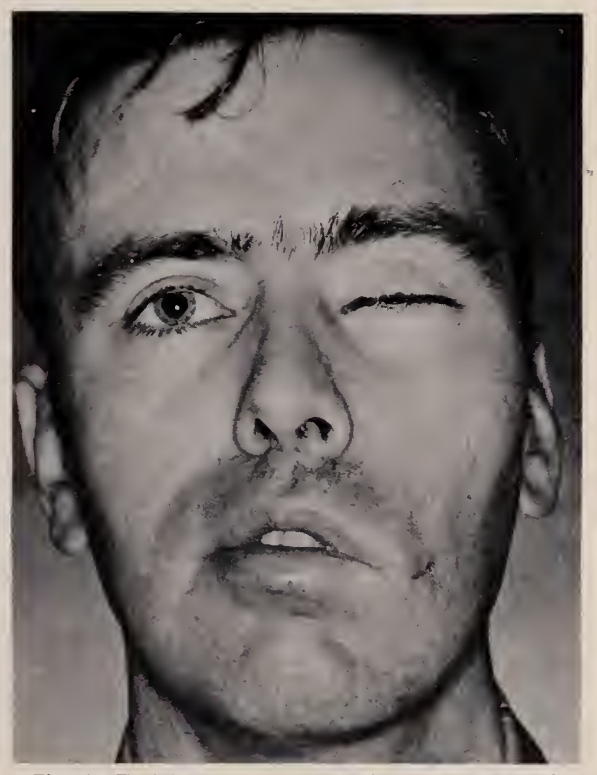


Fig. 4—Facial appearance of patient 10 months after virtually complete removal of a clivus meningioma. Residual left facial palsy is slight after cosmetic sling operation. The left lid is surgically closed to protect the cornea. Note flattening of left forehead due to lack of frontalis muscle innervation. (Patient has given his permission to use this photograph.)

vivors have been few. Suboccipital decompression has previously been the most frequently recommended treatment. However, in view of our experience with the present case and the fact that all such tumors have been globular rather than *en plaque,* surgical removal should be considered.

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From A Doctor's Journal

Nov. 18, 1891—Examined 14 pensioners yesterday. An interesting case has been in court this week. Dr. Willis T. Honsinger of West Chazy has been sued by a man named Pike for malpractice. Over three years ago Pike broke his kneepan, or rather ruptured its ligament. He got the ordinary ligamentous union and a serviceable limb. He was probably induced to sue, thinking he might get some money out of the doctor, perhaps without a trial. Drs. A. M. Phelps of New York, A. P. Grinnell of Burlington, Drs. Madden and Schuyler of Plattsburgh testified as to the proper treatment that Dr. Honsinger had given.

Dr. Irwin of Malone was the expert for the prosecution. He made a pitiful appearance, not knowing what he was talking about. After the testimony was in, the Court directed the jury to bring in a verdict of no cause for action. By the plaintiff's own testimony of his expert it was shown that the plaintiff's ligamentous kneepan was in no manner due to the defendant's neglect or want of skill. It was also shown that the defendant was unusually attentive and that the result was average.*

*David S. Kellogg, M.D.: A Doctor at All Hours, edited by Allan Everest, 1970.

Cover Photo

Duck Slough

The 35 mm slide of the cover photo was taken by Doctor Rodger Lundblad on a duck hunting expedition to Big Stone County near Ortonville, Minnesota, in October, 1970.

Doctor Lundblad is a urologist on the staff of Hennepin County General Hospital and a clinical instructor in the Department of Urology at the University of Minnesota, as well as in private practice in Minneapolis.

The photo was taken on Kodachrome II film with a Nikkormat FTN at F4 and 1/50 sec. near dusk.

If you want a thing well done, don't do it yourself unless you know how.—Optimist

Regional Enteritis and Down's Syndrome

JOHN N. BURGESS, M.B., F.R.C.S.* AND KEITH A. KELLY, M.D.†

SOME OBSERVERS have suggested that emotional or psychiatric factors play a part in the etiology of chronic regional enteritis,[1,2] although others have denied this.[3] In view of this controversy, we thought it of interest to record the occurrence of this disease in a patient with Down's syndrome.

Case Report

A 24-year-old white woman was first seen at the Mayo Clinic for evaluation of abdominal pain. She was the product of a nine-month normal pregnancy and was the third child of a 40-year-old mother. The other two children were living and well. There was no family history of Down's syndrome or intestinal disorders. A diagnosis of Down's syndrome had been established in the patient at the age of seven months. She was severely retarded mentally and required custodial care and special schooling. However, she had been in good general health until two years before being seen at the Mayo Clinic when she began having attacks of cramping, midabdominal pain. The attacks lasted two to seven hours, usually began one to three hours after meals, occurred three to four times a month, and were occasionally relieved by belching, vomiting, or the application of hot packs. Her bowels generally moved once daily and the movements were of normal size, color, and consistency. A diagnosis of "nervous stomach" had been made prior to her coming to the Mayo Clinic and tranquilizers and various "antigas" medications had been prescribed. However, her symptoms continued unabated and nine weeks before she was seen here they became much more frequent and severe. The attacks now occurred almost daily. Although her appetite remained good, she had lost 10 pounds over the previous two months.

Past History

Past history disclosed that a heart murmur had been noted at birth, but the patient had no symptoms referable to the cardiovascular or respiratory systems. Menses were scanty and irregular.

Physical Examination

On physical examination she appeared younger than her age and looked chronically but not acutely ill. She was mentally retarded, but happy, agreeable, and placid, and generally made light of her disease and of painful experiences. However, she occasionally appeared anxious and fearful in the hospital setting, and at these times she required and was reassured by the presence of her mother. Her height was four feet, seven inches, weight 88 pounds, pulse rate 84/min. and temperature 98.6 F. The physical findings of Down's syndrome were present, including the characteristic facies, Brushfield spots, brachycephaly, coarse pale skin, incurved little fingers, increased space between the first and second toes, and generalized muscular hypotonicity. She had an internal strabismus of the right eye and a grade 2/6 soft systolic cardiac murmur most prominent at the left sternal border at the level of the third intercostal space. The lower quadrants of the abdomen were distended and tender, but there was no rebound tenderness. No masses were palpable. Bowel sounds were few and high-pitched. Rectal examination showed moderate tenderness on the left side, but no masses were palpable.

Laboratory Findings

Laboratory findings were as follows: hemoglobin 10.0 gm/100 ml; erythrocytes 3,980,000/cu mm, with anisocytosis and poikilocytosis, and a hypochromic, microcytic



Fig. 1—Roentgenogram of abdomen taken during examination of small intestine with aid of barium. Areas of narrowing and dilatation seen in distal small bowel.

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†Mayo Clinic and Mayo Foundation: Department of Surgery.

picture; erythrocyte sedimentation rate 36 mm in one hour; serum iron 30 μg; serum proteins (gm/100 ml): albumin 1.27, α_1-globulin 1.27, α_2-globulin 0.54, β-globulin 0.57, γ-globulin 1.54, and total proteins 4.26 gm/ml; serum carotene 13 μg/100 ml; other blood tests and urinalysis normal; and stools positive for blood (guaiac test) and for fatty acid crystals and oil droplets (fatty stool). Electrocardiography, proctoscopy, and chest roentgenography gave normal results. Plain roentgenograms of the abdomen with the patient upright and in decubitus showed a collection of gas and fluid in the midabdomen compatible with a partial mechanical small-bowel obstruction. Barium examination of the small bowel showed multiple areas of narrowing and constriction in the mid and lower parts of the ileum with alternate zones of dilatation (Figure 1). Barium examination of the colon showed minimal mucosal ulceration of the cecum and ascending colon.

Diagnosis

A diagnosis of regional enteritis of the small bowel and colon with partial small-bowel obstruction was made and abdominal exploration advised. At operation multiple areas of thickened, fibrotic, narrowed small bowel were found beginning 150 cm distal to the ligament of Treitz and extending 90 cm to a point 30 cm proximal to the ileocecal valve. Interspaced between these regions of narrowing were dilated areas. The adjacent mesentery was thickened, firm, edematous, and crowded up around the bowel wall in a "pannus" formation. Numerous large, firm lymph nodes were present in the mesentery. The walls of the cecum and ascending colon were also slightly thickened and fibrotic but the remainder of the colon was normal. The involved area of small intestine was resected and an end-to-end jejunoileostomy was performed.

The pathologist reported regional enteritis with mucosal ulceration and transmural inflammation involving the entire resected segment of small bowel with multiple "skip" areas of regional dilatation (Figure 2).

The patient recovered uneventfully from operation.



Fig. 2—Histologic section of ileum showing extensive mucosal ulceration and transmural chronic inflammation compatible with chronic regional enteritis. (x100.)

Discussion

This report is the first that we know of describing the occurrence of chronic regional enteritis in a patient with Down's syndrome. Other gastrointestinal disorders, however, have been associated with Down's anomaly, such as congenital hypertrophic pyloric stenosis,[4] congenital duodenal obstruction,[4,5] duodenal diverticulum,[6] Hirschsprung's disease,[7] and chronic nonspecific ulcerative colitis.[8]

The psyche has been implicated in the etiology of regional enteritis. Stewart,[1] in a series of 82 patients, showed a strong interrelationship between regional enteritis and emotional factors, especially overt fear and repressed rage. Ingelfinger[2] too thought that patients with regional enteritis and ulcerative colitis represented psychiatric problems. Von Patter and colleagues[3] concluded after their exhaustive review of 600 cases of regional enteritis that there was "no reason to believe that the psyche plays more than a modifying role in the course of the disease."

Our patient displayed generally the happy, placid, child-like personality that is typical of Down's syndrome. However, her mental deficiency made it difficult to evaluate underlying emotional conflicts. Certainly emotional disturbances can and do exist in people with Down's anomaly. Thus, the fact that our patient with regional enteritis had Down's anomaly does not rule out an etiologic or modifying role for the psyche in regional enteritis.

References may be secured from the author or the reprints.

Easy street is always a dead-end street or a blind alley.—Herbert Prochnow

Surgical Myocardial Revascularization*

A Follow-Up Study

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J. J. GARAMELLA, M.D., Ph.D., M. F. LYNCH, M.D.,
A. M. BILGUTAY, M.D., Ph.D., AND W. D. KELLY, M.D., Ph.D.

THE QUESTION of the benefits and risks of any treatment can best be answered by restudying those patients who underwent the specific treatment. If a patient has an operation, survival alone is no proof of its value. These considerations seem most appropriate in relation to surgical revascularization of the myocardium.

Materials and Methods

From 1964 to January 9, 1970, our group of cardiovascular surgeons performed myocardial revascularization in 268 patients (464 internal mammary arteries were implanted). No patient has been lost to follow-up. The first 50 patients on whom the study was completed approximately one year after surgery form the basis of this report.

There were 45 men and five women with an average age of 47 years (26-67). The preoperative evaluation included routine laboratory studies (SMA-12), post-prandial blood sugar and blood lipid determinations. Resting electrocardiograms were obtained in all patients, whereas only 26 double Master tests were done as we were often reluctant to exercise patients with clearly abnormal resting electrocardiograms. All patients were studied by left heart catheterizations, left cine ventriculography and selective coronary angiography. The postoperative examinations done one year after surgical revascularizations (seven to 21 months) included these same studies and angiography of the implanted internal mammary arteries. In 47 patients both internal mammary arteries had been implanted; in three only one mammary was inserted. The technique used initially in the series followed the original Vineberg procedure,[1] but was soon modified to that described by Favaloro.[2]

Results

Preoperative Evaluation

Six of these 50 patients were free of angina, yet had suffered at least one previous myocardial infarction. The existence of widespread coronary artery obstruction (severe three-vessel disease) demonstrated in the cine angiograms prompted these operations.

The distribution of the 44 symptomatic patients according to their angina is shown in Figure 1, using a zero-to-four scale. Twenty-six had had a previous myocardial infarction; 32

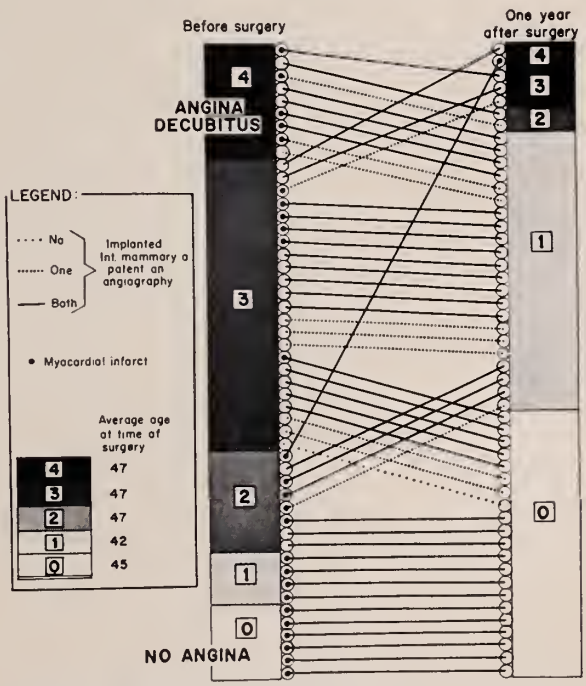


Fig. 1—Angina pectoris in 50 patients before and one year after myocardial revascularization.

*From Northwestern Hospital and its University of Minnesota Medical Unit, Minneapolis, Minnesota.

(Groups Three and Four) were disabled and largely confined to chair or bed.

Twelve patients had an elevation of their serum cholesterol levels above 280 mg. percent, and 15 showed serum triglycerides above 135 mg. percent. In five patients both abnormalities coincided. Twenty-three were so overweight that weight reduction seemed mandatory before surgery, which explains preoperative preparation time of up to 21 months (average 2.6 months), and the lower average weight and lipids at operation (Figure 2). None had hypertension and only one had mild diabetes. Thirteen of the 50 preoperative resting electrocardiograms were read as within normal limits. Five of 26 double Master tests revealed no evidence of myocardial ischemia.

Selective coronary angiography showed in every case that one or more of the following branches was narrowed to more than 90 percent: left anterior descending, circumflex, right coronary. The severity of the angiographically demonstrated coronary arteriosclerosis is reflected in the small number of non-involved arteries found. Only two anterior descending, six circumflex, and five right coronary arteries were found free of serious disease in these 50 patients.

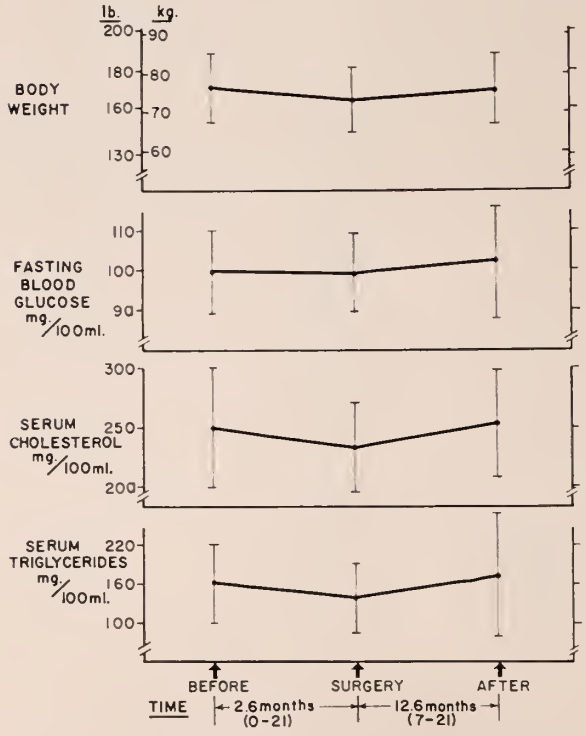


Fig. 2—Average weight, blood sugar and lipid determinations (± standard deviation) in 50 patients before, at time of, and after myocardial revascularization.

Operative Procedure

Surgery was undertaken when the patients were close to their ideal weight, had stopped smoking, and recent (less than six months) myocardial infarction and congestive heart failure had been excluded. In 47 of them, a double implant with both mammary arteries was done. Within the last year, combinations of arterial implants with aorta-to-coronary bypass using saphenous vein grafts have been preferred.[3] These latter patients are included in this study only in relation to the post-surgical mortality (Figure 3).

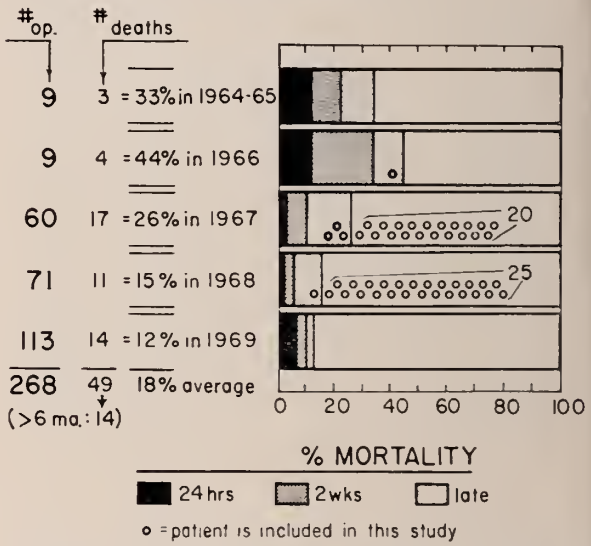


Fig. 3—Mortality in patients with revascularized myocardium. * = patient included in this study.

After discharge from the hospital, the patients have been followed by their referring physicians and seen occasionally by us. No strict drug regimen was followed, but the patients were encouraged to take nitroglycerin if necessary. Anticoagulants were not used after operation.

Postoperative Evaluation

One year (seven to 21 months) after operation, these patients were admitted to the hospital (Northwestern or St. Mary's Hospital, Minneapolis) for two days.

The preoperative evaluation protocol was followed and cine angiograms of the implanted arteries were attempted. For these studies various catheters have been utilized, and in many cases cutdown on both right and left brachial arteries was done in order to introduce the tip of the catheter selectively into the origin of the corresponding mammary artery. We carefully avoided occluding the orifice of the vessel with the

catheter. Five to 10 milliliters of meglumine diatrizoate (Renografin 60%) were hand injected and cine roentgenograms obtained. These film strips were then evaluated by two independent examiners for patency of the vessels, formation of anastomoses and myocardial "blushing."*

In one patient it was felt unwise to catheterize the origin of either of his mammary arteries due to the extreme ease of dissection of the subclavian arterial wall by the catheter tip. Forty-two of the 49 implanted left internal mammary arteries showed a free flow of injected dye as a proof of their patency. In 30 of these, anastomoses within the cardiac shadow were demonstrated. Forty-three out of 48 right internal mammary arteries were shown to be patent by angiography and 29 collateralized with a main coronary vessel.

Lead II has been recorded during injection of the internal mammary arteries and evaluated in the last 12 patients: nine displayed transient changes, predominantly T-wave depressions. Many of the patients experienced anginal pain shortly after injection of dye into the implanted vessels. The slow regression of dye influence on the electrocardiogram explains the abnormalities at the beginning of injection: a "hang-over" from a preceding injection (one to five minutes before) (Figure 4).

The average weight and serum lipid levels were found to have returned close to the pre-preparatory levels in these 50 patients. Patients were able to diet and lose weight and lower their blood fats when goaded by angina, but after surgical relief of angina they resumed their traditional dietary ways (Figure 2).

Whereas 13 of the patients had preoperative normal electrocardiograms, only 10 were found to have normal electrocardiograms one year postoperatively. Seven of these were of the original 13 normals. The changes from normal in the electrocardiograms of these seven patients who were unremarkable preoperatively and no longer within normal limits after operation were not outspoken and could easily be explained on the basis of postoperative nonspecific pericarditis. This also invalidated the majority of postoperative double Master's tests.

Grading the patients' angina one year after operation showed the shift seen in Figure 1. Those six patients who were free of angina during the preoperative period remained so. Of

*Excellent radiographic technique is required to show the small collaterals and accumulations of blood-diluted dye in coronary arteries. Any appreciable over- or under-exposure will wash or burn out these small vessels and low contrast images. Failure to photograph good dye flow from an implanted artery can be bad radiography rather than bad flow.

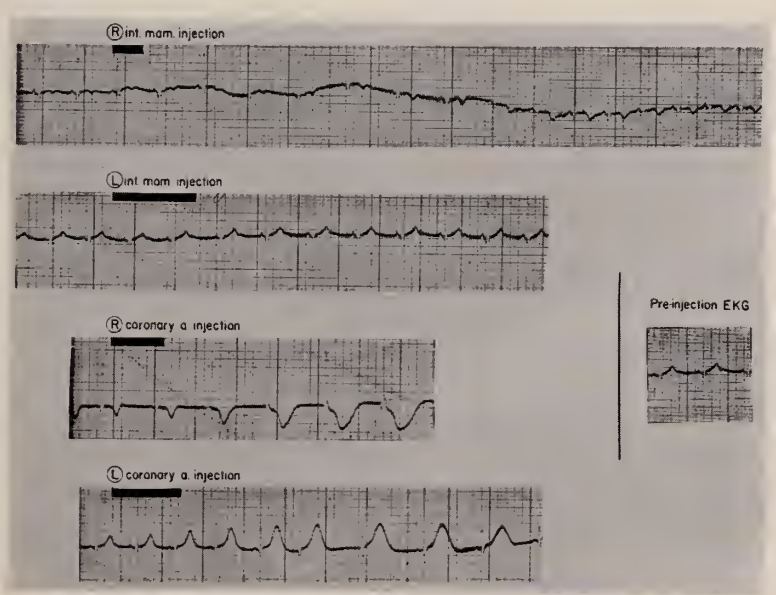


Fig. 4—Electrocardiographic changes induced by angiOgraphy of implanted mammary arteries and of coronary arteries. Patient G. M., (female), born 1926; bilateral internal mammary artery implantation on April 18, 1969. The above-shown tracings (ECG lead II) were all obtained during angiography on March 23, 1970. Marked electrocardiographic changes occurred during all angiograms except those of the implanted left internal mammary artery.

the total group, two patients stated that they felt about the same as before surgery, and two others said that they felt worse. One of them suffered from a myocardial infarction 15 months after operation (his implants were angiographically patent previously and showed good anastomoses). Thirty-three of the 50 patients went back to work four to six months after operation.

Mortality

The distribution of operative and postoperative mortality is shown in Figure 3. Note that the late mortality includes 14 patients who died from a variety of diseases more than six months after operation. Five of these 14 patients died more than one year after operation (Table).

Discussion

This study confirms Vineberg's discovery that the implantation of extracardiac arteries into ischemic heart muscle is a feasible way to treat angina pectoris. Vineberg pointed out that it takes about four to six months before collaterals between implanted arteries and the coronaries are formed.[1] This time interval coincides remarkably with the resumption of work by 33 of our patients. A recent cooperative statistical evaluation of 1,755 patients who underwent bilateral internal mammary implantation shows that 80% were definitely benefited by the operation.[4]

At present, primary aorta-to-coronary vein graft bypass procedures are preferred when feasible as they provide immediate myocardial perfusion. A successful revascularization by a vein graft can be done only if a major coronary artery shows proximal occlusion with distal patency. All revascularization procedures make sense only when viable, ischemic myocardium can be benefited and saved.

This postoperative evaluation remains incomplete, as better objective criteria are needed to judge fully as to success or failure of the implant operation. The subjective feeling of improvement may be quite gratifying but may not totally exclude a placebo effect. However, it is unlikely that a patient can be so benefited by any sham operation that he returns from bed confinement to work as a switchman (Patient 5, Table).

Good evidence about the operative result may be obtained from selective angiography. We found 88% of implanted internal mammary arteries to be patent and to show flow on dye injection. More than patency is desired, however; better that collaterals and anastomoses within the heart be displayed. Evidence for the latter was demonstrated in 61% of all implanted vessels. Fulton's studies of occlusive coronary heart disease by post-mortem angiography correlated with anatomical dissections show that an extensive secondary anastomosing arteriolar circulation develops in the ischemic myocardium.[5] Implanted systemic arteries pulled into tunnels in the ventricular wall revascularize the myocardium by making multiple connections with this system.[6] These vessels are 100-300 microns in diameter and form an angioma arteriole surrounding the implanted artery and interconnecting with the arteriolar system which feeds into the sinusoidal capillary nutrient system of the myocardium. Surplus flow from the implanted arteries backs up

TABLE

INTRA-VITAM AND POST-MORTEM FINDINGS IN FIVE PATIENTS WHO DIED LATE AFTER OPERATIVE MYOCARDIAL REVASCULARIZATION

#	Patient	Age at Death	Interval Op.-Death	Cause of Death	Findings on Autopsy	Preceding Intra-Vitam Findings on Angiography
1.	D. B.	46 y	18 mos.	Acute pancreatitis	Patent left implant	Patent left implant (only one artery implanted)
2.	W. M.	42 y	30 mos.	Suicide	Both implanted mammaries thrombosed	Both implanted mammaries patent.
3.	V. R.	47 y	42 mos.	Cardiac arrhythmia	Implants occluded at site of entry into the myocardium.	Patent without anastomoses.
4.	R. H.	53 y	26 mos.	Shortly after implant of gastroepiploic artery.	Patent left internal mammary with anastomoses.	Patent left internal mammary with anastomoses (right not implanted).
5.	R. S.	57 y	12 mos.	Industrial railway accident	No autopsy possible	Both implanted arteries patent with good anastomoses.

retrograde out of this system into the epicardial supply vessels during systolic compression of myocardial vessels (prearteriolar coronary arteries).

Cine angiography, because of its resolution limitations, visualizes this arteriolar system only as a blush or stain of dye in the myocardium. Discrete vessels are visualized on cine angiograms only when the flow is great enough to provide a surplus so that the large delivery arteries are opacified in a retrograde fashion.

Connections between the implanted arteries and the major coronary arteries are then demonstrated and reported. A myocardial blush with dye visualized in the coronary veins seems to be equally as valid a demonstration of nutritional arterial supply but has been frequently overlooked because it is less dramatic and requires better radiographic photography.

As shown in Figure 1, there is poor correlation between patency of implanted vessels and postoperative angina. It has been observed that some patients with rather poor angiographical results nevertheless showed impressive improvement.[7,8] This may be explained by a placebo effect, but not necessarily so. Lipchik et al.[9] described two patients with proximally occluded internal mammary arteries and distal filling of the implanted vessels via additional anastomoses. There is no present evidence that this mechanism plays a role in any of this group of patients, but the possibility cannot be ignored.

Electrocardiography was disappointing as a tool for follow-up evaluation of the revascularized patients. Postoperative changes are too frequent and obviously related to the surgery on the heart. Some resting electrocardiograms gave the impression of less marked signs of ischemia, yet only three previously abnormal electrocardiograms were read as within normal limits one year after operation. It should not be surprising that the electrocardiogram does not improve along with the patient. New scars in the myocardium were added by the surgery, and pre-existing scars are also at best the same after operation as before.

Nine out of 12 patients studied showed acute transient changes in their electrocardiograms during angiography of their implanted vessels. This means that the dye is interfering with the electrical phenomena in the heart, thus proving communication between these implanted vessels and the heart muscle cell. We do not know if the absence of this sign is significant. It should also be pointed out that similar changes are frequently observed during coronary angiography, where their meaning is not too well defined.[10] An example is given in Figure 4; after injection of contrast medium, the patient reported a transient uncomfortable feeling in the left side of his chest, but he did not label it as the type of angina he had experienced before.

Aorta-to-coronary bypass procedures have been performed extensively in the recent past.[11] We think that indirect revascularization by implanting one or both mammary arteries has its definite place where coronary angiography demonstrates widespread diffuse disease. Furthermore, the venous bypass may well undergo marked atheromatous changes, thereby hampering the additional blood supply.[12]

Conclusion

An additional blood supply can regularly be brought to the myocardium of the ischemic heart. As long as "there is no proof that the best conservative treatment is better than or even as good as surgical management,"[3] carefully selected patients may well be helped by operative myocardial revascularization. We cannot yet answer the question: do these procedures prolong life and prevent subsequent myocardial infarction or failure? But present evidence suggests that the answer will be affirmative.

Summary

Fifty patients have been re-evaluated one year after internal mammary artery implantation. Eighty-eight percent of the implanted vessels were angiographically patent, 61 percent with evidence for anastomoses. Forty patients improved after operation; five died later than one year postoperatively. Electrocardiograms do not reflect the clinical situation during the follow-up of these patients. Changes of body weight and blood lipids cannot explain the patients' improvement.

We wish to express gratitude to our colleagues at Northwestern Hospital and at St. Mary's Hospital, Minneapolis, for allowing us to use some data and information obtained by them.

References may be secured from the author or the reprints.

The first forty years of life gives us the text; the next thirty supply the commentary.
—Arthur Schopenhauer

The Calendar*

For these following days are from counselling Jove. In the first place, the first, the fourth, and the seventh, is a holy day: the eighth and ninth, these are two days, I ween, of the month far advancing, for getting ready the works of mortals, and the eleventh and twelfth, both in truth are good, the one for shearing sheep, the other for reaping laughing corn: but the twelfth is far better than the eleventh, for on it, look you, the high-hovering spider spins his threads in the long summer day, when also the wise ant harvests his heap. On this day, too, a woman should set up her loom, and put forth her work. But on the thirteenth of the beginning of the month avoid commencing your sowing: though to set plants it is best.

The sixteenth, however, is very unprofitable to plants, but auspicious for the birth of men, though for a girl it is not propitious, either to be first born, or to be joined in wedlock. Nor, in truth, is the first sixth day suitable for the birth of girls, but a favorable day for cutting kids and flocks of sheep . . . On the eighth of the month emasculate the boar and loud bellowing bull, and on the twelfth the toil-enduring mules. But on the longest twentieth day, in broad day, generate a wise man, for he will be very cautious of mind. And lucky for raising sons is the tenth day, and the fourteenth for girls. On this, too, tame sheep, and trailing-footed, crumple-horned oxen, and sharp-toothed dog, and patient mules, applying your hand to them.

Then on the fourth of the month lead home a bride, after having examined the omens, which are best in this matter. But avoid the fifth days, since they are both mischievous and destructive . . . On the seventeenth watch well, and cast upon the well-rounded thrashing floor Demeter's holy gift; and let the wood-cutter cut timbers for chamber furniture, and many blocks for naval purposes, which are fit for ships. And on the fourth begin to put together slight vessels. But the nineteenth is a better day towards evening. And the first ninth day in a month is wholly harmless to mortals; since lucky indeed is this day for planting and for birth, to man as well as woman; and never is it a day altogether bad. Now few, again, know that the twenty-ninth of the month is best both for broaching a cask, and placing a yoke on the neck of oxen and mules and fleet-footed steeds . . . On the fourth day open your cask: the fourteenth day is a day sacred beyond all others: and few know that the fourth after the twentieth of the month is best, at the break of day: but toward evening it is worse. These days indeed are to men on the earth a great benefit. But the others falling between are harmless, bringing nothing of moment. One man praises one day, another another. But few know them. Blest and fortunate is he who knowingly does all these things with reference to these days, unblamed by the immortals, discerning omens, and avoiding transgressions.

*From Hesiod's Works and Days.

Balance

Another form of wastefulness is expenditure of words beyond the income of ideas.*

*Maxwell Droke: Speaker's Handbook of Humor.

Proper Use of Oxygen in Respiratory Therapy

JOSEF K. WANG, M.D.*

OXYGEN THERAPY is a well established practice in respiratory care. Yet the morbidity or mortality secondary to improper use of oxygen is relatively high. This paper will discuss the physiological basis and the practical approaches of oxygen therapy.

Oxygen Molecules

Oxygen molecules are utilized in the mitochondria as the final acceptors of the electron transfer system to complete oxidative phosphorylation which is most efficient in producing energy for the cell.

In the body, oxygen is stored in three forms. (1) as a gas, (2) in physical solution and (3) in chemical combination. When the oxygen supply is insufficient, the body uses stored oxygen to retard the rate of change of the oxygen tension in blood and tissues. The storage capacity of the body for oxygen is rather restricted. In terms of oxygen reserve for metabolic purposes, the most important store is that in the arterial blood. Oxygen contained in arterial blood is carried as dissolved oxygen in physical solution and as a chemical compound with hemoglobin in the erythrocytes. The total amount of oxygen contained in arterial blood (oxygen content) is about 20 volume per cent. That in mixed venous blood is 15 volume per cent. This indicates that the mean oxygen uptake of the body is approximately 5 volume per cent. The coronary arteriovenous oxygen difference is found to be 11.5 volume per cent. It appears that oxygen uptake of cardiac muscle is high and its oxygen reserve is exceedingly small. However, in terms of tolerance to hypoxia the brain is the critical tissue, not the heart.[1] The human body depends for life on a continuous supply of oxygen.

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A certain pressure gradient is needed for transfer of oxygen from capillary to tissue. The critical PO_2 of capillary was proposed to be 20 to 30 mm. Hg.[2] In normal man breathing air at sea-level, the inspired PO_2 is about 150 mm. Hg, the alveolar PO_2 100 mm. Hg, the arterial PO_2 90 mm. Hg, and the mixed venous PO_2 about 47 mm. Hg. These data give a mean tissue capillary PO_2 of 51 mm. Hg. Hence, in normal man, the mitochondria assumed to operate at a PO_2 of 10 mm. Hg, are provided with oxygen under a pressure-gradient of 41 mm. Hg.[3]

An arterial PO_2 below 20 mm. Hg seems to be incompatible with life. A tension above 30 mm. Hg (saturation of about 50%) probably maintains adequate cellular function in most tissues, providing blood flow is adequate. The total quantity of oxygen available to the cell is modified by many factors. It has been shown that adequate transport of oxygen to the tissue is no guarantee against oxygen deprivation if oxygen release from the hemoglobin in the tissue is sluggish. For this reason it is unlikely that any particular PO_2 can be considered safe. The patient should be given sufficient oxygen to raise or maintain his arterial PO_2 as close as possible to normal range although it is realized that this may not be achieved.

Oxygen Intoxication

In patients requiring prolonged oxygen therapy, oxygen intoxication of the lung is being suspected with increasing frequency. In humans the toxic dose of oxygen is not known, and clinical observations suggest that tolerance varies with the patient and the disease. The hazard of oxygen intoxication may indicate that the concentration and duration of oxygen be kept to the lowest level compatible with adequate function of vital organs. Means other than raising the inspired PO_2 should be utilized to improve arterial oxygenation. These measures include proper airway toilet and cor-

rection of pulmonary congestion. It has been suggested that avoidance of extremes of lung volume, both high and low, will minimize consumption of alveolar lining material and reduce excessive, edema-producing stress in the lung parenchyma.[4] In patients with severe acute respiratory failure continuous positive-pressure ventilation with a mean end-expiratory pressure of 13 cm. of water has been shown to be effective in improving the arterial oxygenation with relatively low inspired PO_2, although side-effects on hemodynamics often occurred.[5] Proper management of the patient should also provide adequate oxygen-carrying capacity and tissue perfusion. At present the subject of improving oxygen release in the tissue is bristling with unconfirmed speculations.

Arterial Hypoxemia

Oxygen therapy is indicated whenever arterial hypoxemia occurs. The three types of hypoxemia that can be corrected by breathing an oxygen-enriched gas mixture are those due to hypoventilation, to impaired diffusion, and to abnormal ventilation perfusion ratios in the lung. Oxygen therapy may also be helpful as a temporary measure to minimize the arterial hypoxemia, to a limited extent, resulting from right-to-left shunts.

Alveolar hypoventilation secondary to analgesic agents can cause hypoxemia. The hypoventilation that follows a period of hyperventilation and anesthesia can result in a definite lowering of arterial PO_2, if air is breathed after operation.[6] Thus, administration of oxygen is indicated during the post-anesthesia period.

Most shock patients have an extremely low PO_2 except in the uncomplicated oligemic shock. Reduced arterial PO_2 is common in patients with myocardial infarction, presumably due to abnormal ventilation perfusion ratios in the lung and pulmonary edema. Although the breathing of oxygen-enriched gas mixture leads to an increased systemic vascular resistance and mean arterial pressure in acute myocardial infarction, some patients have an increased cardiac output after oxygen administration.[8]. Theoretically, high inspired PO_2 given to this patient may increase the mean capillary PO_2 thus improve the oxygen delivery to mitochondria.[3] Hypoxemia due to respiratory insufficiency in combat casualties responded favorably to oxygen therapy.[9] The routine administration of oxygen to all patients with acute myocardial infarction or shock seems to be justified.

Pre-existing chronic obstructive lung disease often reveals chronic hypercapnia with hypoxemia. The most significant cause of hypoxemia in these patients is believed to be ventilation perfusion imbalance.[10] If the status of hypercapnia is prolonged and severe, respiratory control may be predominantly dependent on a hypoxic drive. In these patients, acute exacerbation of the chronic lung disease or depressant effect of anesthetic or analgesic drugs further suppresses the CO_2-sensitive respiratory central chemoreceptors. An indiscriminate use of oxygen under these circumstances leads to a severe hypoventilation, the dangerous development of CO_2 retention, and eventually to CO_2 narcosis. However, this potential hazard should not keep us from using oxygen for the following reasons: (1) Hypoxia is often damaging to the cells; hypercapnia rarely is. (2) The controlled application of oxygen, using a variety of devices,[11,12,13] will greatly reduce the threat of anoxia without serious CO_2 retention in most cases.[12,13,14,15,16,17] (3) Frequent measurements of P CO_2, particularly during the first two hours of oxygen therapy, and the availability of mechanical ventilation can timelily reverse the progressive hypercapnia.

Oxygen Therapy

The ideal starting concentration for oxygen therapy is probably 24-25%, for arterial oxygen saturation is often largely improved with little increase in arterial P CO_2.[17] Inspired oxygen concentration can gradually be increased so that a compromise is reached between a satisfactory arterial PO_2 and a slight rise in P CO_2. If dangerous CO_2 retention ($>$20 mm. Hg above original P CO_2) does occur in an oxygenated patient, ventilatory assistance is required.

If patients have been inadvertently given uncontrolled high-concentration oxygen therapy and have already developed a severe hypercapnia, withdrawal of oxygen or substitution by a low concentration of oxygen may prove hazardous. A withdrawal of oxygen in this instance may lead to a more intense hypoxemia than if oxygen had never been administered at all. This so-called "intermittent oxygen therapy" is a practice resembling that of bringing a drowning man to the surface of the water occasionally.[18] For this type of patient, optimal oxygen concentration must be maintained and ventilatory assistance be instituted. Continuous oxygen therapy in chronic

respiratory insufficiency with hypoxemia has been shown to prolong life in some patients,[19] and to reverse the pulmonary hypertension[20,21] and hypoxia-induced polycythemia.[22] Although convincing evidence of its value is still lacking, it seems reasonable to give an extended trial to long-term domiciliary oxygen treatment. The chronic bronchitic patients form the majority of those who may need oxygen therapy at home. The danger of high concentration of oxygen in the bronchitic with CO_2 retention is well known. Controlled oxygen therapy (25-30%) should therefore be provided as the standard equipment for routine home use. An initial close observation in the hospital may also be indicated.

Summary

Oxygen therapy is indicated whenever hypoxemia occurs, provided the breathing of oxygen-enriched gas mixture can improve the hypoxemia. In most cases, oxygen administration does improve the arterial oxygenation without serious complication. The principle of oxygen therapy is to provide continuous and controlled administration of optimal oxygen concentration. In practice a compromise must be reached between adequate tissue oxygenation and oxygen toxicity also between optimal arterial oxygenation and CO_2 retention.

The major ingredients of correct management of the acutely ill hypoxemic patient should include maintenance of optimal ventilation of the lungs and repeated observation of arterial P O_2, P CO_2 and pH.

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Cigarettes

Our American Medical Association Journal recently announced that 4,500 new teen-agers each day become addicts of cigarettes. That means there are over 1,500,000 two-legged sheep who have been stampeded annually into shortening their lives by a minimum of 5 years apiece.*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

Common sense is, of all kinds, the most uncommon.—Tryon Edwards

Laboratory Letter

The Pill and Thyroid Function

We shall discuss the interpretation of laboratory tests—the hows, the whys, the pitfalls, the possibilities, and the meanings. A test result is not merely a number, but the measured end of a process that may shift with age, disease, drugs, and conditions of blood drawing. Physicians, then, must evaluate such numbers in context. Through these letters, perhaps we can help in a small way to shape that context.

Occasionally a physician has asked us why PBI and T-3 results don't jibe in women on oral contraceptives. What brands, he wanted to know, were responsible? How high did drugs push the PBI? How much could they depress the T-3? How should he approach thyroid function in women on hormones?

All good questions. Here is a go at the answers. First, though, a few scraps of important information? 1) Most thyroxine binds to globulin in serum; less than 0.1% goes unbound, or "free". 2) PBI measures mostly the iodine attached to this globulin. 3) The amount of globulin inversely affects the T-3 value (the more globulin circulating, the less radioactive tri-iodo-thyronine "taken up"). When a woman takes birth control pills, estrogen in the pills increases that portion of protein to which thyroxine clings, thereby forcing the **PBI** up and the **T-3** down.

To get at the other answers, we recently went over the drug histories of 50 women on contraceptive pills who had high PBIs and low T-3s. Types of pills included C-Quens, Enovid and Enovid-E, Norinyl and Norinyl-1, Orth-o-Novum, Ovulen, and Provest. Thus, all the commonly used agents exerted a thyroid effect. And a significant one, too. Values for PBI ran from 8.1 mcg.% to 21.0 meg.% (mean 10.1 mcg.%) and for T-3 from 24% to 8% (mean 19%).

Yet when we multiplied PBI by T-3 to get a Free Thyroxine Index:

PBI	×	T-3	=	FTI
(4-8 mcg.%)		(25-35%)		(100-280)

forty-eight patients fell in the euthyroid range. From this and other studies, we are convinced the Index reliably measures thyroid status when patients have drug or disease-induced protein charges.

Up to this point, we have not mentioned two other serum tests: T-4 by column chromatography and "free" T-4 by a mixed isotope dilution method. We shall do so now. In our hands, the T-4 column test, though accurate and precise enough, has not solved the pill problem.* Like PBI, estrogen sends it up. And, like PBI, drugs containing organic or inorganic iodine, will cause high results. Theoretically, "free" T-4 ought to be the answer since globulin changes do not influence it. But it is more expensive than a PBI and T-3 together, gives about the same information,[1] and, at least in the Mayo Clinic experience, "distinguished poorly between different levels of thyroid funtion."[2]

Richard L. Reece, M.D.
Minneapolis, Minnesota

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September, 1968

*Since this letter was written, we have abandoned the T-4 column test because it did not eliminate the problem of iodine and iodide contamination. Instead we use the T-4 by Murphy-Patte method. Although the T-4 by this method is not affected by contamination, it too is increased by oral contraceptive.

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If you think old soldiers just fade away, try getting into your old Army uniform.
—Herald, Bradenton, Fla.



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Editorials

Acquired Heart Disease: A Surgeon's View

OPEN HEART SURGERY techniques rest on a sound physiological basis, and operative mortality has dropped dramatically over the past 10 years. The by-pass technique has been simplified and the requirement of blood for priming and replacement has been greatly reduced. Much of this surgery can be carried out without resorting to elaborate (and expensive) diagnostic procedures, e. g., cardiac catheterization, angiocardiography.

Selecting Patients

The surgeon and internist often can decide whether the patient requires open heart surgery after taking a history, performing a physical, doing an electrocardiogram and fluoroscoping the heart. The most important part of this process is the history since the physician must judge by the patient's story the severity of the disease. However, in the elderly, syncope, angina and dyspnea may be due to aortic stenosis or cerebral arteriosclerosis and coronary sclerosis. In older people, one must also be mindful of misleading physical findings. For example, trivial aortic valve sclerosis can mimic the murmur of aortic stenosis. Electrocardiographic findings of left ventricular conduction defects, myocardial infarction and left ventricular hypertrophy may be present either singly or in multiple combinations in the elderly, further complicating the diagnosis of left ventricular outflow tract obstruction.

Mitral Stenosis

If disabled patients with mitral stenosis have a pliable valve, they may be treated safely and with good results by closed transventricular valvotomy. Functional Class I patients who have a second embolus while being adequately anticoagulated are also candidates for closed valvotomy. If the patient falls into the Class III category of functional disability and the valve is immobile and calcified, then open heart surgery is indicated and the valve will probably have to be replaced.

Closed transventricular mitral valvotomy is an excellent procedure in properly selected patients with mitral stenosis. Before 1960, long-term results differed considerably from what we can achieve now. This is for two reasons: (1) Improved selection of patients, (2) improved valvotomy techniques. Patients selected for this procedure must have a pliable mitral valve with a good opening and closing snap, no calcium in the valve at cardiac fluoroscopy, no murmur of mitral insufficiency, and absence of significant associated valve disease.

With the use of the transventricular dilator, rather than transatrial techniques, the risk of the operation has fallen to one-to-two per cent. The transventricular dilator assures an adequate opening and reduces the risk of dislodging a clot. No longer does the surgeon need to worry about excessively manipulating the atrium or lacerating its wall. The likelihood of recurrent mitral stenosis in these patients is low.

Subjecting the patients with pliable mitral stenosis to an open cardiac procedure, as has been suggested by some, adds unnecessarily to the complexity of the procedure.



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Mitral Valve Repair

Before a satisfactory functioning mitral valve prosthesis was developed, many mitral valve repair techniques were attempted. Now that reliable prosthesis are available, repair techniques have been largely abandoned. Although ideally a central orifice mitral valve would be best, this still is an area of active clinical investigation.

At least two of these techniques, when the anatomic pathology is appropriate, are sound procedures. First, the posterior medial annuloplasty as described by Merindino, and second, repair of ruptured chordae tendineae as described by McGoon. The opportunity to use the second procedure occurs oftener than one might expect. The recent onset of mitral insufficiency in an adult patient is often the result of ruptured chordae tendineae. However, if significant valvular calcification is present, when there is significant destruction of the substance of the anterior mitral leaflet, or when severe subchordal fusion is present, none of these repair techniques are likely to succeed.

Repair techniques avoid the problems of a malfunctioning prosthesis as well as the risks of thrombo-embolism. With better valvular prosthetics, these repair techniques may be abandoned eventually.

Patients with mitral valve incompetence from ruptured chordae tendineae are low operative risks. Patients with chronic pulmonary venous hypertension, reduced pulmonary compliance, pulmonary artery hypertension, right ventricular dilatation and tricuspid incompetence—the hallmarks of severe chronic mitral valve disease—have a lesser chance of surviving surgery. The use of potent diuretics, digitalis, salt restriction and limited activity often allows patients with mitral valve disease to live many years with moderate to marked disability. The clinical decision as to the precise time of surgical intervention in these patients requires the frequent interaction among the surgeon, the cardiologist and the patient.

Aortic Stenosis

The diagnosis of calcific aortic stenosis can, in most patients, be clearly defined by the symptom complex of angina, syncope or dyspnea in a patient with an aortic systolic ejection murmur, electrocardiographic evidence of left ventricular hypertrophy and the fluoroscopic finding of a calcified aortic valve. In these patients, cardiac catheterization is unnecessary.

The risk of aortic valve replacement is probably unrelated to the degree of coronary artery disease in most patients. It is more affected by the problem of resuturing a diseased aorta. The risk is greater in the elderly patient or in the patient who has associated hypertension.

Embolism in the early postoperative period and dehiscence of the valve prosthesis may occur if the surgeon inadequately debrides the aortic root before he implants the prosthesis. Good long-term results depend upon adequate debridement and careful multiple suture technique.

The type of aortic prosthesis used is probably less important than the technique of inserting it. An aortic hemograft has a place in treating aortic valve disease, but we have not come to use it routinely primarily because of the uncertainty of long-term results. In those patients who can be treated with antocoagulant therapy, the operative risk, the predictability of hemodynamic function, as well as long-term results, favor the prosthetic valve in the routine case where replacement is required. In well selected patients, aortic valve replacement may be performed with an operative mortality of three-to-five percent.

Surgical Treatment of Coronary Artery Disease

Though early enthusiasm for the Vineberg procedure has subsided, more direct techniques to revascularize the myocardium show promise. In the patient who has severe angina because of localized obstruction of either the right or the left coronary artery, direct shunting procedures from the aorta to the distal coronary vessel are reasonable operative procedures. As much as 100 cc. per minute of blood flow can be delivered to the myocardium by these direct shunting procedures. Ultimately, results of direct shunting procedures may rest with the technical ability of the surgeon to perform a small anastomosis that will remain patent. Early results of the aorto-coronary by-pass shunt look promising indeed. Data to support long-term results is, as yet, lacking.

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Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., certain elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—they can both cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

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mitral incompetence, ventricular aneurysm with left ventricular failure, or ventricular septal defect with large left-to-right shunt can be repaired with good hemodynamic results. Indeed, even extensive excision of dyskinetic left ventricular myocardium may be possible. But, just as many attempts to resect the small left ventricular aneurysm have carried high operative mortality, so do the current attempts to resect poorly functioning left ventricular myocardium. Once again, we urge caution in selecting such patients, since the operative mortality may closely parallel the survival rate in the non-operated patients with extensive disease. As with those other surgical procedures which have been associated with "a wave of enthusiasm," time will put matters in their proper perspective.

Bacterial Endocarditis

Although most patients with acute and subacute bacterial endocarditis respond satisfactorily to intensive medical management, occasionally either the mitral or the aortic valve is damaged to the point that severe hemodynamic derangement results. Optimally, if the valve could be sterilized by appropriate antibiotics, subsequent surgical correction could be carried out with predictably good results. If the patient is dying from an incompetent valve, but still has positive cultures, surgery may be the only recourse to prevent death. The use of an aortic homograft in this latter instance can be expected to heal even though the infection has not been controlled.

In summary, open cardiac surgery has been established on a sound physiologic basis. In those areas where adequate repair techniques are available, results are predictably excellent. Considering the open heart procedures as a group, the overall risk is about ten percent.

Joseph C. Kiser, M.D.
Minneapolis, Minnesota

Progressive Anterior Horn Cell Disease

Progressive anterior horn cell disease in childhood is arbitrarily designated *Werdnig-Hoffman* disease if onset is before two years of age, and *Kugelberg-Welander* disease if onset is between two years of age and the late teens.[1] The clinical course is directly related to the age of onset. Children who are born with obvious weakness, or develop weakness during the first two months of life, usually are dead by age two, and rarely live past age four. On the other hand, children who are normal for the first two months of life and develop weakness between two and twelve months of age, usually are able to sit and may walk with the use of braces. They often live into the second decade. Children who develop their first symptoms between one year and two years of age frequently are able to stand and walk with help and their life expectancy may run several decades. It is not clear in what manner these diseases are related to progressive spinal muscular atrophy of adults. Because etiology is unknown it is impossible to speak intelligently about the interrelationship of these entities.

In recent years it has been demonstrated that there is an increase of activity of the oxidative enzymes in the anterior horn cells of children with Werdnig-Hoffman disease.[2] Electron microscopic studies reveal abnormalities present in axons which impinge upon the anterior horn cells.[3] An increased number of mitochondria were also noted in the anterior horn cells, which explains the enzyme changes. It is therefore possible that degeneration of the anterior horn cells is a phenomenon secondary to disease of axons of the internuncial neurons, or of some more rostral segment of the corticospinal pathway.

These diseases are transmitted on a hereditary basis and usually as autosomal recessive traits. It is therefore likely that a biochemical defect or defects will eventually be uncovered.

Kenneth F. Swaiman, M.D.*
Minneapolis, Minnesota

*Professor and Director, Pediatric Neurology, University of Minnesota Medical School.

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3. Chou, S. M., and Fakadej, A. V.: Ultrastructure of chromatolytic motoneurons in a case of Werdnig-Hoffman disease. Neurology 20:381, 1970.

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The Challenge of the Compound Fracture*

THE COMPOUND FRACTURE may excite the intern and resident, create havoc in an emergency room, or stir up controversies between medical services or physicians treating the injured patient. To the experienced practitioner who has witnessed the countless times that stretchers glide past the operating room door, frequently bearing the same patients, this complex injury remains a challenge which he mutely accepts. "War is the only proper school for the surgeon" reflects the wisdom of Hippocrates, and this is a truth to which, unhappily, many of our modern day surgeons can attest. Ancient and modern techniques developed by observation of mass casualties or by the lonely observer frequently are lost to the general medical population and hence to the population as a whole.

One of the great triumphs of medical and surgical management of the compound fracture has been the development of tetanus immunization. This is perhaps the best taught medical lesson of World War I. In successive wars, the rapid transport of the critically injured patient with a compound fracture to a center where management can be undertaken has been a major factor in the survival of these victims. The dramatic change in survival statistics, even on comparison of the Vietnam and Korean conflicts, is an exciting lesson. In a nation where more than 100,000 accidental deaths (50,000 of them due to automobile accidents) and more than 10,000,000 disabling injuries occur annually, we still do not have the universal capability to transport the severely injured patient safely and rapidly. Neither do we have adequate regional trauma centers where personnel, both medical and paramedical, can manage trauma efficiently and safely. Rapid transportation in terms of adequate ambulance services in the highly populated areas and helicopter and flight service in the most remote areas, not to speak of simple communication lines to expedite their use, are not available. The soldier on the battlefield probably has a better statistical chance of survival than the automobile-injured patient in the middle of Minnesota.

With the development of rapid transportation systems and trauma centers, we could concentrate on the really exciting element—the management of the compound fracture. "The healing power of nature" may be paramount in managing these injuries. The greatest advances, however, will be our ability to assist this power of nature. When we know what disruptions are taking place in these fractures in terms of gross, cellular, and molecular levels, then we can learn to reverse these disruptions. Whether our treatment in the future will hinge upon the rapid fixation of fractures by implantation of metals, ceramics, or other media, transplantation of bones, reimplantation or transplantation of limbs, soft tissue management by insertion of plastic tendons, restoration of nerves and vessels, the use of proper fluids, electrolytes, and other support media, or combinations of these methods remains to be seen. All the foregoing will become commonplace when we know how to assist "nature" in its work.

Not the pulsatile flow of blood from open vessels and the grating of ends of broken bone but rather the knowledge and ability to restore, with rapidity, the form and function to an injured limb will be the true excitement of the resident of the future and a great satisfaction to the practitioner. We should be that part of history which will teach posterity these lessons.

*See page 853.

†Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Rudolph A. Klassen, M.D.†
Rochester, Minnesota

The greatest of faults, I should say, is to be conscious of none.—Thomas Carlyle

You can do very little with faith, but you can do nothing without it.—Samuel Butler

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Successful Treatment of End-Stage Renal Failure "Down-Under and in Northlands"

THE ARTICLE on successful treatment of end-stage renal failure by Sheil and co-workers* of Sydney, Australia, again calls attention to the remarkable progress made in recent years in the treatment of an otherwise fatal disease and provides some interesting contrasts for our program in Minnesota.

In the Australian program, all patients presenting with renal failure were accepted for treatment unless absolute medical contraindications for renal transplantation existed. Similar broadening of criteria for selection of patients has occurred in our region as the results of treatment have improved. Simmons and co-workers recently proposed in a previous issue of this journal that the only absolute contraindication for renal transplantation was widespread, rapidly progressive malignancy. Certainly some relative contraindications exist, which render a successful outcome so unlikely as not to justify the effort and expense involved. Insufficient experience is available at this point in renal transplantation of patients of advanced age and in those with rapidly progressive systemic diseases to state with assurance when renal transplantation is or is not justified, especially if organs from living donors are used for such purposes. It will be necessary, therefore, to continue to use good clinical judgment in the selection of patients for dialysis and transplantation.

The exclusive use of cadaver kidneys in Sydney, Australia, avoided many of the moral, social, and psychological problems associated with the use of living donors. Unfortunately, availability of kidneys for this purpose has been extremely limited in our state, and our transplantation programs are heavily dependent on the availability of consanguineous donors. This approach is justified by the significantly higher allograft survival rates when living donors are used. Even with current methods of immunosuppressive therapy, use of antilymphocytic globulin, and tissue histocompatibility matching, allograft survival rates are 20% higher at two years when consanguineous kidneys rather than cadaver kidneys are used. On the other hand, if the results of cadaver organ transplantation improve substantially, it will be difficult to justify the continued use of living donors.

The impressive number of cadaver organs available in Sydney, Australia, from a population smaller than that of Minnesota points out the main deficiency in our current program—failure to obtain cadaver organs. Because cadaver organ procurement was so successful in the former program, the pool of recipients awaiting renal transplantation appeared to be relatively small (39 patients) and the patients requiring treatment each year (45/1,000,000 population) could be accommodated in a relatively small dialysis program. In our state, the number of patients maintained by hemodialysis had grown to 175 in January 1971; most of these patients were maintained in hospital units at considerable cost.

If a high proportion of cadaver allografts continue to function for five years or more and if availability of organs from cadaver sources can be substantially increased, it would appear that this approach would provide a more satisfactory and economic form of treatment than long-term hemodialysis. Certainly the current results of cadaver-donor kidney transplantation are sufficiently encouraging to justify concerted effort by all physicians to improve cadaver organ procurement in our state.

William J. Johnson, M.D.†
Rochester, Minnesota

*Sheil, A. G. R., Stewart, J. H., Johnson, J. R., May, J., Sharp, A. M., and Bashir, H.: Cadaver-Donor Renal Transplantation. Minnesota Med 54:463, 1971.

†Mayo Clinic and Mayo Foundation.

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Surgical Myocardial Revascularization

THE REPORT in this issue of MINNESOTA MEDICINE*, *Surgical Myocardial Revascularization,* raises some interesting points. The 50 cases reviewed by Dr. Pierach et al. had internal mammary implantation into the myocardium as a procedure for the relief of angina pectoris. The diligent follow-up of this group of patients is commendable and, indeed, must be a part of our evaluation of new procedures. The marked improvement demonstrated in the level of angina is, indeed, gratifying. This must be interpreted very cautiously, however, in view of the reported 18 percent mortality.

Indeed, the mortality for this procedure (internal mammary implantation) in a large series nationwide, remains in the 10-percent bracket. This is in sharp contrast to the results reported from direct aorto-coronary vein by-pass grafting procedures. The expected mortality here should run well below 5 percent.

It is apparent now that direct aorto-coronary by-pass grafting procedures are preferable to the internal mammary implantation procedure. Mortality figures, as well as postoperative clinical and laboratory evaluations, support this conclusion. Internal mammary implantation into the myocardium may, however, yet have a place in the management of the patient with angina pectoris. Occasionally patients are encountered in whom direct aorto-coronary vein by-pass is not anatomically possible. In these few instances, the implant may be preferable to continued medical management.

Patients with implants and/or direct aorto-coronary by-pass procedures must be studied diligently. After 20 or more years of experience treating coronary patients with anticoagulants, there is still considerable controversy over the efficacy of this form of treatment. Let us not end up 10 years hence without a clear-cut answer on surgical procedures for myocardial revascularization.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

*See page 795.

The Compressionist's Creed

I believe in Trudeau, mighty father of the American sanitarium, maker of heaven on earth for the tuberculous; and in Artificial Pneumothorax; which was conceived by Carson, born of the labors of Forlanini; suffered under Pompous Pride and Prejudice; was criticized by the Cranks whose patients are dead and buried; thousands now well, even in their third stage, rose again from their bed; ascending into the Heaven of Medicine's Immortals, they sit on the right hand of Hippocrates our Father; from thence do they judge these phthisiotherapists quick to collapse cavities or dead on their job.

I believe in Bodington, Brehmer, Koch and Brauer, in Murphy, Friedrich, Wilms Sauerbruch, Stuerz and Jacobeus, in the unforgiveness of the sins of Omission in Collapse Therapy, and in the resurrection of a healthy body from a diseased one, and long life for the tuberculous with care everlasting. Amen.*

*A. C. Corcoran, M.D.: A Mirror up to Medicine, 1961.

"The Compressionist's Creed" was composed by a Dr. Norman Bethune, specialist in chest diseases, particularly tuberculosis, at the Royal Victoria Hospital in Montreal and was put up on the wall of the Chest Clinic there, wherefrom a pious colleague ripped it down because he considered it "sacrilegious."

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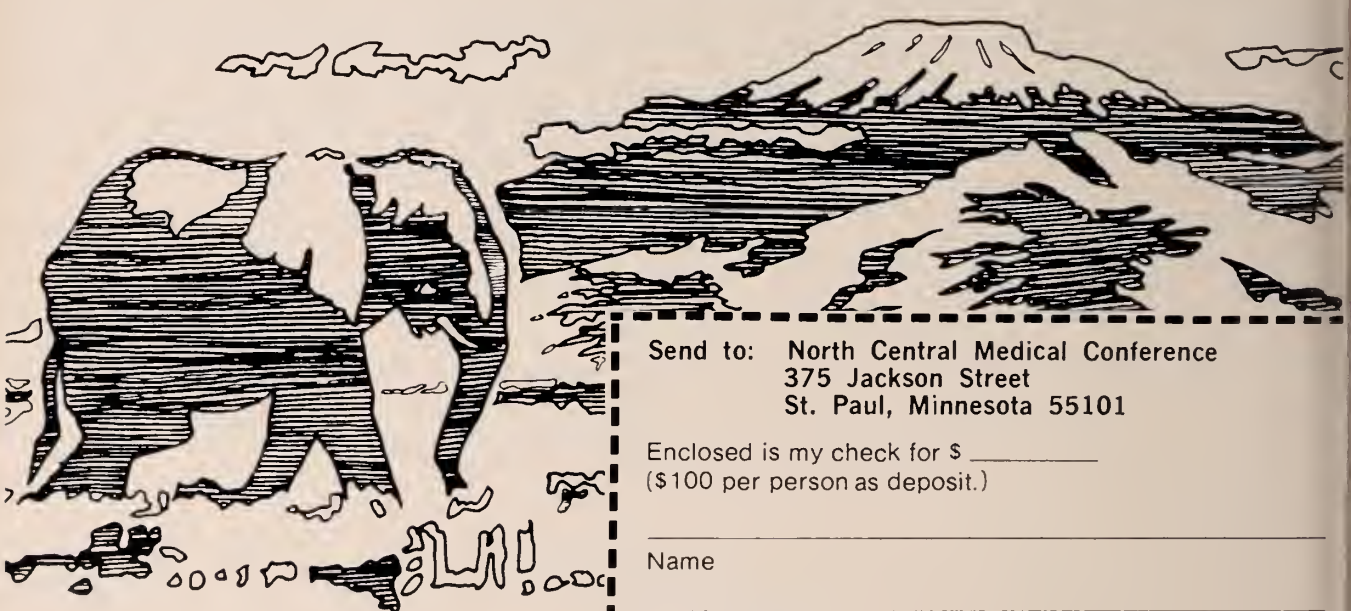
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Radiographic Skull Examinations

As a "moon-lighter" in a suburban Twin City hospital emergency room, I have "soliloquized" on innumerable occasions about the doctor's dilemma you have so aptly described in the March issue of MINNESOTA MEDICINE.* I have often wondered about the tremendous cost of ordering a host of radiographic examinations following trivial trauma. It is heartening to note that this thought has also occurred to prominent members of the Medical Community. Discussing the "utility and futility" of radiographic skull examinations, Doctors Bell and Loop state, " . . . . . physicians fear that for not discovering a clinically occult fracture they are liable to malpractice suits sufficiently harrassing and costly to justify virtually endless medically unindicated examinations."† Since I am still in training and do not have my own private patients, I fail to grasp the severity of such medicolegal indications.

Perhaps, after having an unfortunate personal experience, I will feel less uncomfortable contributing to this extravaganza.

Incidentally, since the devaluation of the rupee several years ago, a lakh of rupees now amount to only $13,333. approximately ($1 = 7.5 rupees)—unless you were referring to the Pakistani rupee!

Surendra Sethi, M.D.
St. Paul, Minnesota

*The Editor's Soliloquy: For a Thousand Rupees. Minnesota Med 54:205, 1971.
†Bell, R. S. and Loop, J. W.: The Utility and Futility of Radiographic Skull Examinations for Trauma. New Engl J Med 284:236, 1971.

Lithium

I noted the interesting "Laboratory Letter" about lithium, in the June issue* of MINNESOTA MEDICINE. There are two points that I would like to make, regarding this topic:

(1) In the Fieve and Platman study, the lack of baseline scans on their patients raised doubts as to the validity of results. It is interesting that in a later article† the same authors reported a similar incidence of goiter in 13 patients treated with imipramine (no lithium). While it is true that lithium may be goiterogenic, the incidence of thyroid abnormalities in lithium-treated subjects probably is closer to that reported by Schou et al‡ 12 out of a series of 330.

(2) Fortunately, none of the marketed dosage forms of lithium carbonate, including our flesh-colored capsules, contain erythrosine dye or iodine. The capsules studied by Doctor Haas (your reference no. 3) were "clear pink" and did contain significant amounts of the dye. That type of capsule, in the beginning, was selected by numerous clinical investigators, but was never considered for marketing.

I hasten to add that my comments are not meant to alter the conclusion (last sentence) of your article. Life with lithium is not as easy as with many other drugs, but it certainly is a Godsend to properly selected patients.

Ben E. Greenwell, Ph.D.
Baudette, Minnesota

*Page 420.
†Amer J. Psychiat 125:149, April 10, 1969
‡Brit Med J. 3:710, Sep. 21, 1968



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Editor's Soliloquy

American Medicine

In his arraignment of American medicine some of the statements made by medical student Michael G. Michaelson* seem to be either grotesquely biased or a construct of his own naivete. He has not yet graduated into the maturity of a practicing physician, the position from which medicine must be truly evaluated as well as dispensed.

This country, he claims, "is, by the majority of available standards, an unhealthy nation." He uses no other indices, however, than the infant mortality (nineteenth in the world) and the life expectancy (sixteenth) whereby to denounce us as being "behind every major industrial nation in the world." Among other absurd charges he maintains that "diseases that ought to have been eradicated years and even decades ago remain formidable threats; millions of Americans live in needless pain or die preventable deaths; health care is fragmented, inefficient, inequitable, inhumane and, too often, of questionable quality." One wonders: is he completely oblivious of the fact that within the past few 'decades' such dreaded diseases, epidemics and plagues as smallpox, diphtheria, typhoid fever, yellow fever, malaria, poliomyelitis, tuberculosis, rabies, pneumonia, mastoiditis, osteomyelitis, septicemia and a host of others either have been almost completely eradicated or have successfully responded to specific drugs or methods of immunization? With these modern advances in the science of medicine, it is hard to conceive how anyone could stigmatize us as an "unhealthy nation." I recommend to him the reading of some of the medical practices in Africa and India: a first-hand observation of the bureaucratically or hierarchically controlled medicine of some of the Eurasian countries.

He then goes on to charge that it is in the "sphere of financing" that "medical malpractice descends from the—unintelligent to—the criminal." Apparently he is appalled or outraged at the idea that citizens must pay for their own health care which "is very, very expensive." Is he completely unaware of the fact that through Medicare, Medicaid and prepaid medical and surgical insurance of one type or another medical and hospital care is available to so high a percentage of people that the major onus of an unwelcome and unexpected illness is largely relieved by these guaranties? An analysis of health-care costs for 1968 revealed that approximately 80% of the population of Minnesota† is covered to some extent by prepaid medical insurance, and that the average for the nation is about the same.

Surely no significant portion of the medical profession would object to one hundred percent of populace coverage by prepayment plans, though government-controlled, tax-financed, prepaid and bureaucratized medicine would be the most expensive that could be devised. Of course Michaelson recognizes that hospital employees must be paid for their services and also that there are very few people who do not, in a time of critical illness, recommend that the doctor or the hospital "spare no expense." The significance of this should be obvious.

Rather than die in the "modern Intensive Care Units"—where patients need not die in "technological dependency and superb electrolyte imbalance" as

*The American Scholar, Autumn 1970, 39:4:694—Phi Beta Kappa
†Blue Cross-Blue Shield.

Michaelson seems to imply, would he rather save the "$300 or $400" that it costs than give the critically-ill individual an opportunity to survive?

It may be that Michaelson has confused medical care with the poor health that results from the numerous ecological violations committed by some industry and some agriculture practices: pollution of air, water, soil; and from the bad health practices of individuals: over-eating, over-drinking, over-smoking, over-indulgence in self-medicated drugs, tranquilizers, pep pills, and various other excesses. These pernicious habits have no direct relevance to medical care and are totally beyond the control of our public health agencies; nor can they be completely abolished by legislation. Their abrogation is the responsibility of everyone, individually and collectively, not specifically that of physicians or the health system.

Medical student Michaelson queries why "any one of us have to pay for what is a basic human right" and he charges that "certainly the poor are treated like animals or machines by health professionals in this country. In the United States every patient, and not merely every poor patient, is a nigger."—His statement, not mine, nor ours!—Further, he opines that every physician of intelligence and social sensitivity clearly must believe: that "the American Medical Association as a political force in this country should be discredited and, if possible, destroyed." Certainly Michaelson understands bureaucratization well enough to realize that to destroy one system and produce a counter-organization of health professionals would create nothing more than another national bureaucracy to the end that eventually the whole nation would become a committee to control the committees that dictate to the committees ad infinitum.

Paradoxically, Michaelson both praises and condemns us when he refers to us as model ("archetypal") Americans, omnipotent and omniscient, self-sufficient, independent, rugged individuals, but essentially obsolete as physicians. Apparently he is either forgetting or disregarding the fact that through our constant daily re-education via the numerous sources of medical literature, conferences, seminars, symposia, and scientific medical meetings, most of us have probably forgotten or discarded more knowledge of medicine and the American health care system than he, Michaelson, can ever learn by studying only one of its numerous facets. Hopefully he will develop a greater degree of maturity when he pursues, for his Doctor of Philosophy degree, any particular field of medicine he chooses to enter.

Carl O. Rice, M.D.

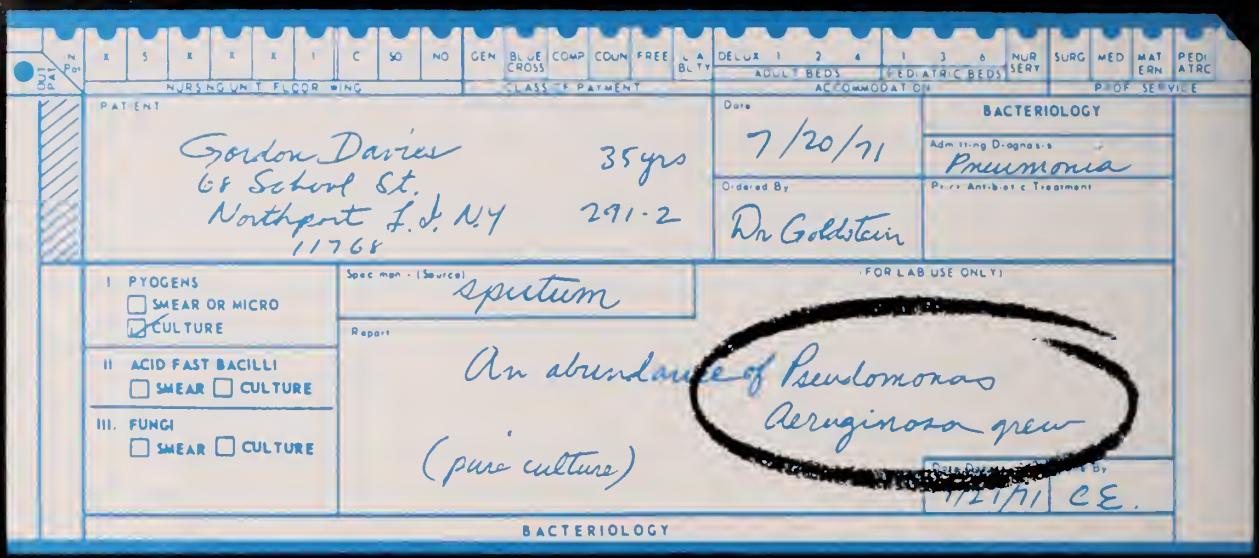
OLD DOC HESS SAYS: Only mediocrities can emerge in a system that will not tolerate wave makers.

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The Hennepin County Academy of General Practice, Annual Invitational Banquet will be held on Monday evening November 15, 1971 at the Radisson Hotel Downtown. The social hour will begin at 6:00 p.m. with dinner scheduled for 7:30 p.m. Dr. Harlen Hatcher will present "The Developing Great Lakes Megalopolis: A 25 Year Deadline." All metropolitan and out-of-town physicians and their guests are invited. Contact: P. A. Williams, M.D., 3900 Stinson Blvd. N.E., Minneapolis, MN. 55421, or telephone 788-6753.

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Not stable in the presence of penicillinase. *Klebsiella* species are resistant. Some strains of *Pseudomonas* have developed resistance fairly rapidly. **Contraindications:** Known penicillin allergy. **Warnings:** Serious and occasional fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. 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Observe patients with renal impairment for bleeding manifestations and adhere strictly to dosage recommendations. If bleeding manifestations appear, discontinue antibiotic and institute appropriate therapy. As with any penicillin preparation, the possibility of an allergic response, including anaphylaxis, may occur, particularly in a hypersensitive individual. **Administration:** Intramuscular injections should be made well within the body of a relatively large muscle (not into the lower and mid-third of the upper arm), and aspiration is necessary to help avoid inadvertent injection into a blood vessel. May be given by either intravenous injection or intravenous infusion. 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Didactic

Cysts in the Floor of the Mouth

EUGENE RONTAL, M.D.*, GEORGE L. ADAMS, M.D.* AND
LAWRENCE R. BOIES, JR., M.D.*

THE OCCURRENCE of cystic structures in the floor of the mouth is not rare. All too frequently, however, unfamiliarity with the variety of possible pathologic entities in this anatomic region leads to both an erroneous diagnosis and an inappropriate therapeutic approach. The purpose of this paper is to describe a recent case in point and to call attention to the diagnostic possibilities.

Case Reports

This nine-year-old white female presented at St. Paul-Ramsey Hospital with a one-year history of a painless, cystic mass beneath the chin (Figure 1). There were no systemic symptoms. The patient was otherwise asymptomatic.

On physical examination the mass was particularly noticeable under the chin on swallowing and presented into the floor of the mouth. This structure was 3 x 3 x 5 cm, cystic and freely movable. There was no evidence of inflammation, and there was no abnormal cervical adenopathy. Routine laboratory and radiologic examinations were normal.

On 8-23-70 the patient was taken to the operating room and given general anesthesia via a nasotracheal tube. The cystic mass was removed intact through an intra-oral approach posterior to the orifices to Wharton's ducts (Figure 2). The ducts themselves were not connected with the mass and were undisturbed by the procedure. The patient had an uneventful postoperative course. There has been no evidence of recurrence on follow-up examinations.

Histologic examination showed a cystic, fluid-filled structure with a squamous epithelial lining and sebaceous glands, a picture compatible with the diagnosis of a dermoid cyst (Figure 3).

Discussion

The diagnosis of cystic masses in the floor of the mouth usually can be made by evaluation of anatomic location and a knowledge of the pathogenesis of the diagnostic possibilities. In each case several entities should always come to mind.

*From the Department of Otolaryngology, University of Minnesota Medical School, Minneapolis and St. Paul Ramsey Hospital, St. Paul.
Reprint requests to Department of Otolaryngology, St. Paul-Ramsey Hospital, St. Paul, Minn. 55101.

Ranula

This term has frequently been misused as a generalized classification for all cystic structures in the floor of the mouth; however, it is a distinct clinical entity, referring to those cysts secondary to obstruction of the sublingual ducts.[1] Usually the disease is limited to the floor of the mouth, but cases have been reported of massive ranulas extending into the neck. The treatment of choice is surgical excision. However, if they cannot be completely excised, they may respond to more conservative management such as marsupialization.[2]



Fig. 1—External appearance of the cyst on swallowing.

Cystic Hygroma

This cystic structure appears early in life, generally before two years of age. It is usually smooth, compressible, and can be transilluminated easily. Frequently the skin overlying the mass may turn a bluish color. The origin of such cysts is still debatable, but overgrowth of sequestered embryonic lymph buds is thought to be a good possibility. The cystic hygroma usually presents in the posterior cervical triangle but may originate in the submental or submaxillary regions of the neck, thus entering in the differential diagnosis discussed here. Though excision may be difficult, surgical extirpation is the only recommended treatment.[4] Although occasionally it may regress spontaneously, it is not suggested that a long observation period be allowed in these cases due to the possibility of severe infection or sudden hemorrhage into the cyst, causing respiratory obstruction.

Thyroglossal Duct Cyst

A midline cyst of the neck, this embryonic malformation may present in the submental region mimicking a cyst in the floor of the mouth. Embryologically these cysts represent persistence of the thyroglossal duct which originates between the first and second branchial arches. Their characteristic midline position, motion in the vertical direction on swallowing and episodes of recurrent infection mark the clinical features of these cysts. Treatment is surgical and requires excision of a portion of the hyoid bone with the continued dissection to the base of the tongue to ensure total removal.[5]

Dermoid and Epidermoid Cysts

New reported in his study that dermoids of the head and neck comprise six percent of all dermoids.[1] Of this head and neck group, those situated in the floor of the mouth comprise around 23 percent.[1] It appears that these cysts arise as epidermal inclusions or rests caught between the fusing lingual swellings of the first branchial arch.[6] Though there is some confusion in the literature between epidermoid and dermoid cysts, it is generally conceded that all cysts lined by squamous epithelium and possessing dermal elements, such as sebaceous glands, hair and other skin appendages, are considered to be dermoid cysts.[7] Epidermoid cysts do occur in the floor of the mouth; however, the term epidermoid should be reserved for those cysts which are lined by stratified squamous epithelium and contain concentric rings of keratin, e.g., epidermoid inclusion cysts.[7,8] Epidermoid cysts are usually traumatic in origin. The findings in the patient presented above are compatible with the diagnosis of dermoid cyst which must be considered in all patients with movable cystic structures in the floor of the mouth. The treatment is surgical excision through an extra-oral or intra-oral approach as described in this case.

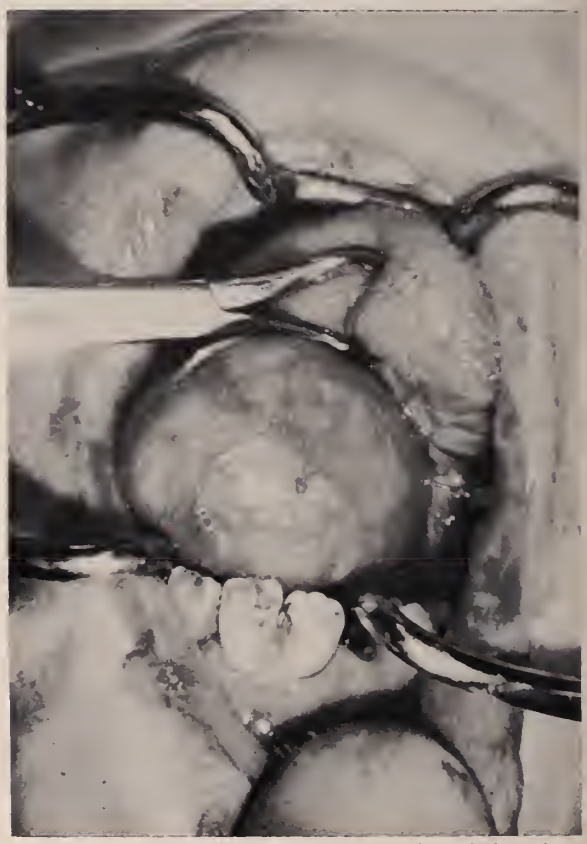


Fig. 2—Intra-oral removal of the cyst from below the tongue.

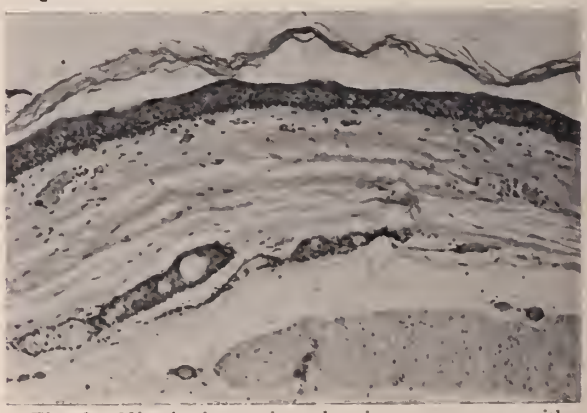


Fig. 3—Histologic section showing squamous epithelium and sebaceous glands.

Miscellaneous Types

Other cysts in the head and neck may enlarge significantly to encroach on the area of the floor of the mouth producing some confusion in diagnosis.[8] These are represented by branchial cleft and congenital laryngeal cysts. However, the characteristic locations of branchial cysts along the anterior border of the sternocleidomastoid muscle and the respiratory symptoms of dyspnea and stridor caused by laryngeal cysts rarely make the diagnosis difficult.[1]

Summary

Inadequate knowledge of the diagnostic possibilities of cystic structures of the floor of the mouth may result in inappropriate therapeutic approaches. A case report of a cystic structure in this area is reported. The diagnostic possibilities are discussed. This differential diagnosis should include ranula, cystic hygroma, thyroglossal duct cyst, dermoid cyst, and more rarely branchial cleft and congenital laryngeal cysts.

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Editors Note: MINNESOTA MEDICINE sincerly thanks you for your confidence in the Journal.

C. O. R.

Friendship is a union of spirits, a marriage of hearts, and the bond thereof virtue.
—William Penn

Alcoholism

Treatment of the Hospitalized Alcoholic

Detoxification and Rehabilitation*

ROBERT M. MORSE, M.D.†

DESPITE STATISTICS which emphasize its major significance, alcoholism remains one of our most neglected illnesses. It ranks among the top four public health problems in our nation, along with heart disease, mental illness, and cancer. According to FBI records, 40% of all arrests are associated with public drunkenness. More than half of our highway fatalities are caused by drunk driving; and recent studies indicate that the driver is usually a bona-fide alcoholic, not just a social drinker coming home from his occasional night out. The alcoholic's increased susceptibility to many diseases has frequently been underscored, as has his decreased life expectancy.

Yet we physicians have been reluctant to treat the alcoholic. This situation may be traced to a number of factors. Even now we often fail to educate our student doctors about the treatment of alcoholism per se, and expose them only to its complications: cirrhosis, delirium tremens, etc. Many of us have become discouraged over past failures in treating alcoholics and are, therefore, pessimistic about the problem. Many of us are uneasy and unclear about our own concepts of alcoholism: whether or not it is a true "disease" or just a bad habit; what causes it; and, most importantly, what if anything, cures it.

The American Medical Association has attempted to alleviate some of our anxieties by providing guidelines from time to time. A statement in 1956, reaffirmed in 1966, made it clear that alcoholism was considered an illness and, as such, a medical responsibility. Use of hospital facilities was encouraged. The Committee on Alcoholism and Drug Dependency reiterated these words in 1969: it emphasized that exactly the same criteria are applicable to the alcohol-dependent person as to any other ill person when hospitalization is being considered as a requisite to medical management. Admission of the alcoholic to general medical services is suggested when he is undergoing a withdrawal syndrome or even when he requests withdrawal, either for the first time or following a relapse. The Committee further recommended that psychiatric units *need* be used only if the patient is overtly psychotic, severely depressed and suicidal, or presents a severe management problem.

In the papers which constitute this symposium we are fortunate to be able to present the opinions of a number of professionals who are devoting much of their time to the treatment of the hospitalized (and the nonhospitalized) alcoholic.

*Symposium on treatment of hospitalized alcoholic presented at the combined meeting of the Mayo Clinic staff and the Zumbro Valley Medical Society on November 4, 1970.

†Department of Psychiatry and Clinical Psychology, Mayo Clinic, Rochester.

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*Dr. George Crane: The Quotable Dr. Crane, 1968.



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Dermatology

Acne Vulgaris and Oral Contraceptives

RECENTLY ATTENTION has been directed towards the safety of the various oral contraceptives now currently in use. Naturally, the question of their use in the control of acne vulgaris must be considered.

Sebum, which is the secretory product of the sebaceous gland, is generally held responsible for the inflammatory nature of the acne papule or lesion. This substance contains free fatty acids, glycerides, waxes, esters, cholesterol, aliphatic alcohols, and squalene. Of these substances, free fatty acids, especially chain lengths C_8 to C_{14}, have been implicated in the cause of the acne lesion. These free fatty acids when injected into human skin (intradermal) produce histologic changes approximating those found in acne. In addition, these substances have been demonstrated to penetrate the epidermal barrier. All this, of course, is only indirect evidence for sebum being the causative factor in acne.

Androgens are known to have a stimulatory effect on the sebaceous gland In fact, they are probably responsible for early development of this cutaneous appendage. On the other hand, estrogens suppress the gland's secretion. It is not surprising then that women on progestin-estrogen drugs should experience decreased sebaceous gland activity. However, it is only the estrogen component which is responsible for inhibiting sebaceous activity. The suppression by estrogen is not rapid; its effect may not be noted till the second or third cycle, occasionally later. At times glandular activity may return even though the patient is still on the hormone. Once estrogen is withdrawn, sebaceous activity returns to normal.

Side effects to the oral contraceptives are well known. With respect to the skin, several aspects should be emphasized. First, in those patients receiving oral estrogens who have had little or no prior acne problem, cessation of the hormone has been occasionally noted to coincide with the onset of acne vulgaris. As previously stated, sebaceous secretion may return to normal while on the hormone and with it the acne. In some patients there appears to be little or no benefit at any time during the therapy. Finally, it must be remembered that this treatment is suppressive and not curative.

In view of the recent suspicions concerning this hormonal drug, its use in acne should probably not be initiated at this time until further data are collected. The only exception might be the severe scarring form of the disease in which all other treatment has failed and permanent disfigurement as well as psychological damage is resulting. In less severe cases the physician has numerous therapeutic choices available to him today.

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Good Advice

"Don't worry" is a better motto if you add the word "others."*

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*Maxwell Droke: Speaker's Handbook of Humor.

The Viewing Box

Respiratory Infections and Diarrhea

THIS 26-YEAR-OLD white male was evaluated because of persistent respiratory infection and diarrhea. Nasal stuffiness, a nonproductive cough, pharyngitis and fatigue had been present approximately four months, accompanied by diarrhea consisting of three to five semiformed stools daily. The stools did not float, were not fatty or foul-smelling, and were negative for ova, parasites and occult blood. Physical examination was normal with no areas of increased pigmentation on the lips, buccal mucosa or fingers.

A barium enema demonstrated a normal colon, but there were multiple nodules in the mucosal pattern of the terminal ileum (Figure 1). The small bowel series (Figure 2) confirmed that the mucosa of the ileum was studded with tiny, uniformly distributed polypoid nodules measuring 2 to 3 mm. in diameter. The mucosal fold pattern was normal.

What is your diagnosis? (See next page.)



Figure 1



Figure 2

Diagnosis Dysgammaglobulinemia with nodular lymphoid hyperplasia of the small intestine.

Immunoelectrophoresis demonstrated dysgammaglobulinemia with virtual absence of the immunoglobulins IgA and IgM and a low normal IgG immunoglobulin. A small intestine biopsy revealed a normal mucosal architecture and localized lymphoid aggregates in the mucosa. The hypertrophied lymphoid tissue produces the nodules seen radiographically.

The findings of dysgammaglobulinemia, multiple small lymphoid nodules in the small intestine, diarrhea, and susceptibility to respiratory infection characterize a syndrome called "dysgammaglobulinemia with nodular lymphoid hyperplasia of the submucosa of the small intestine."[1] Many of the patients with this syndrome also have Giardia lamblia in their stools.[1] The jejunum is usually the area of greatest involvement with the tiny nodular filling defects. However, the entire small intestine may be involved.[2]

Treatment with tetracyclines may achieve remission of the diarrhea. Long-term follow-up is indicated because there is an increased incidence of carcinoma of the stomach and colon among individuals with this syndrome.[1,2] The tiny filling defects in the small intestine may persist for years and remain essentially unchanged.[2]

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Tell the truth, and so puzzle and confound your adversaries.—Henry Wotton.

Neurological Conference

Parkinson's Syndrome

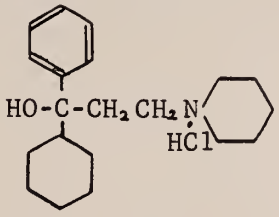
Recent Progress in the Medical Treatment and Its Pharmacological Basis

HIROSHI SHIBASAKI, M.D.*

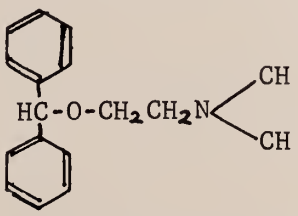
PARKINSONISM or Parkinson's syndrome is commonly regarded as a degenerative disease of later life, manifesting primarily with akinesia, rigidity and tremor.[2,4,5,7] The common pathological findings involve the substantia nigra, corpus striatum, locus caeruleus, globus pallidus and to some degree, the cerebral cortex.[6] According to Hull,[3] the prevalence rate of Parkinson's disease in U.S.A. is 87 to 157 per 100,000 population, so that there are 174,000 to 314,000 patients at present, and about 30,000 new cases are estimated to occur each year. Parkinsonism is usually classified into: (1) the idiopathic form or paralysis agitans, (2) the post-encephalitic form and (3) symptomatic parkinsonism such as cerebral arteriosclerosis, carbon monoxide poisoning and manganese poisoning. It is also well known that administration of phenothiazines and reserpine can cause similar manifestations. In this discussion, Parkinson's syndrome designates (1) and (2), unless otherwise specified.

Generally speaking, the treatment of parkinsonism consists of medical treatment, surgical treatment, physical therapy, and psychological and social care. Medical treatment is classified into: (1) atropine-like drugs, (2) antihistaminic drugs, (3) imipramine derivatives, (4) amantadine, and (5) l-DOPA. Most of the conventional anti-parkinsonian drugs have been used on the empirical basis.[1,8] The purpose of this paper is to review the medical treatment of parkinsonism with particular reference to recent progress made with l-DOPA.

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Trihexyphenidyl (Artane)



Diphenhydramine (Benadryl)

Fig. 1—Structural formula of trihexyphenidyl and diphenhydramine.

Atropine-Like Drugs and Their Mechanisms

This group is one of the most commonly used anti-parkinsonian drug groups and includes Artane, Cogentin, Pagitane, Kemadrin and Akineton. It was about 20 years ago that Doshay et al.[11,12] first reported the effectiveness of trihexyphenidyl (Artane) (Figure 1) in all types of parkinsonism and against all symptoms of parkinsonism. Side effects were relatively rare. It is commonly used in doses of 4 to 6 mg. per day, usually in combination with other drugs.

Benztropine methanesulfonate (Cogentin) is also a frequently used atropine-like drug, with daily dose of 1 to 3 mg. *Side effects* of these atropine-like drugs include headache, giddiness, blurred vision, mydriasis, dry mouth, epigastric distress, and nausea. The side reactions of special pertinence to neurologists are disorientation, confusion and marked agitation. Contraindications to use of these drugs are glaucoma and disorders of the urinary tract as in the case of atropine. The mechanism by which these atropine-like, parasympatholytic agents influence the parkinsonian symptoms is unknown, but Duvoisin[14,15] proposed a direct and mutual antagonism of physostigmine and anticholinergic agents on the clinical manifestations of parkinsonism based on his observation of exacerbation in 17 cases among 20 patients who were given 1 mg. physostigmine intravenously and also of its antagonism with anticholinergic agents. As shown in Figure 2, physostigmine, an anticholinesterase compound, blocks cholinesterase, resulting in an increased cholinergic action, while anticholinergic medication antagonizes the excitatory function of acetylcholine. Dill et al.[10] in 1968 reported that stimulation of corpus striatum with acetylcholine in rats produced increased discharge rate of neurones and contralateral dyskinesia. As the striatum is known to be a site of the cholinergic system, anticholinergic agents seem to inhibit its striatal excitatory activity, resulting in amelioration of the symptoms.

Snyder and Coyle[9] in 1969 reported an interesting observation by using a radioisotope technique applied to the homogenates of rat corpus striatum. They examined the rate of uptake of C^{14}—labelled dopamine at the synapses of corpus striatum, and found that a variety of anti-parkinsonian drugs, including trihexyphenidyl and diphenhydramine, are potent inhibitors of dopamine uptake into synaptosome (Figure 3). When dopamine reuptake is inhibited at the synaptic membrane, it results in potentiation of the synaptic actions of dopamine.

Antihistaminic Drugs and Their Mechanisms

This group includes Benadryl, Disipal, Phenoxene and Benacine. Diphenhydramine (Benadryl) was also used empirically, and known to be more effect-

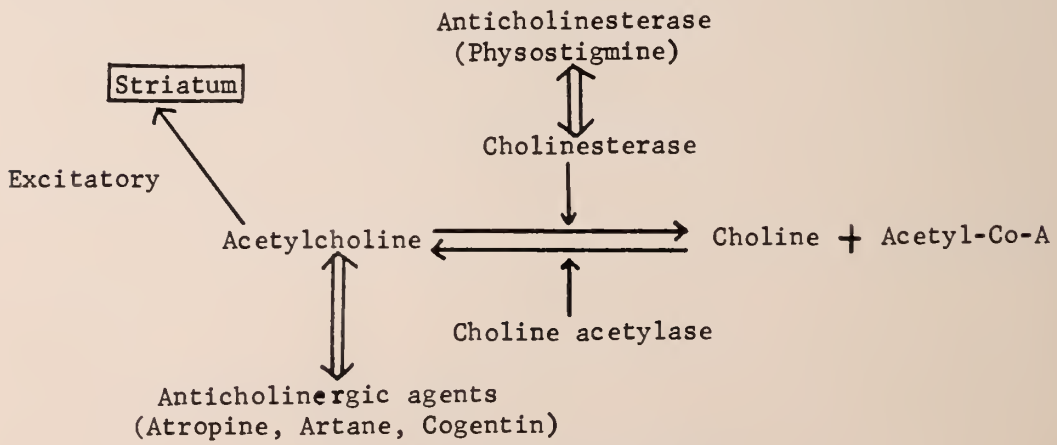


Fig. 2—Metabolism of cholinergic system.

tive on tremor than on rigidity. This is usually administered in doses of 25 to 50 mg. orally three times daily. The side effects are less significant, being produced by its sedative properties. Although its mechanism in suppressing the parkinsonian syndrome is not clear, Duncan,[13] who reported his investigation in "Nature" in 1966, concluded that antihistaminic drugs affect the nerve membrane and work as membrane stabilizers of nerves. On the other hand, it is also known that antihistaminic agents produce cholinergic block, so that the mechanism of anti-parkinsonian actions might be the same as that of atropine-like drugs. Diphenhydramine was also shown to inhibit reuptake of dopamine into the synaptosome, as described above.[9]

Imipramine Derivatives and Their Mechanisms

Imipramine hydrochloride (Tofranil) is known to be an antidepressive agent. Its beneficial effect on parkinsonism was first reported by Sigwald et al.[17] in 1959. More recently Pohlmeier et al.[16] treated 10 patients with desmethylimipramine, Pertofrane, in doses of 75 to 150 mg. daily by oral administration with good results. A varity of *toxic effects* can, however, result from the use of imipramine. These include cardiovascular effects, such as hypotension and syncope, and psychiatric complications such as visual hallucinations, tremor, increased sweating and dry mouth. Pohlmeier[16] speculated that its action might be due to enhancement of the binding of sympathetic neurohumors at receptor sites. However, these tricyclic agents, also, are noted to inhibit the reuptake of dopamine into the synaptosomes like trihexyphenidyl and diphenhydramine (Figure 3).[9]

Amantadine and Its Mechanisms

In 1969, Schwab et al.[25] reported the favorable results of treatment of 163 patients of parkinsonism with amantadine hydrochloride, 1-adamantanamine (Symmetrel). The history of this discovery dates back to April, 1968, when a 58-year-old woman with moderately severe Parkinson's disease was noted to have a remarkable remission in the symptoms while taking amantadine HCl 100 mg. twice daily to prevent influenza. Symmetrel (Figure 4) is an antiribonucleic acid agent and was used as an antiviral agent for Asian (A_2) influenza. According to Schwab's report, 66 percent of the patients among 163 showed subjective or objective improvement of akinesia, rigidity and tremor. Maximum daily dose was

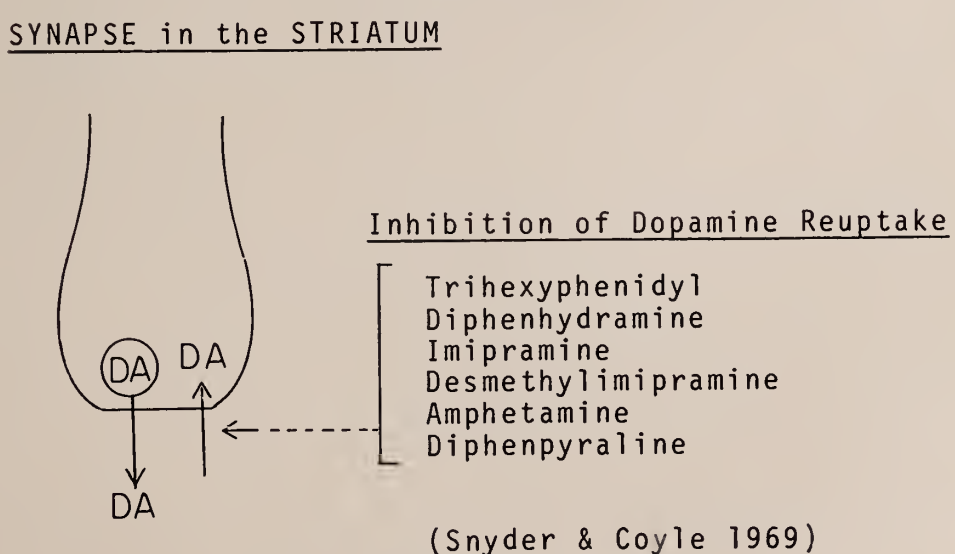
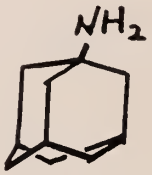


Fig. 3—Inhibition of dopamine reuptake.[9]

200 mg. Among patients with favorable responses, the effect was sustained for three to eight months in 58 percent. In man, this drug is absorbed rapidly and there is nearly complete recovery in unaltered form from the urine.

Side effects were seen in 22 percent of the patients, and consisted of increased jitteriness, insomnia, abdominal uneasiness, dizziness, depression, confusion, and in a few cases, hallucinations. Recently, Parkes et al.[23] confirmed the effect of amantadine by double blind trial. However, Hunter et al.[21] reported very little effect of this agent on parkinsonian disabilities, and found even a deterioration in the functional performance after two to five weeks of treatment in several patients among 17.



1-adamantanamine

Fig. 4—Structural formula of Symmetrel.

The mechanism of amantadine as an anti-viral agent is believed to be due to alteration of the cell membrane which prevents the entry of the virus into the cell. But the mechanism of antiparkinsonian effects is not known. It was found recently by Grelak et al.[20] that this drug does not possess anticholinergic action, although its side effects are somewhat similar to those from atropine-like drugs. It seems to be the recent hypothesis that amantadine inhibits the reuptake of catecholamines in the synaptosomes.[9] In view of amantadine's action as an anti-ribonucleic acid agent there is an interesting fact: Gomirato and Hyden[19] in 1963 reported that ribonucleic acid is increased in the glia and neurones of globus pallidus biopsied from parkinsonian patients at the time of stereotaxic surgery, and among the bases of ribonucleic acid, adenine is increased whereas guanine and uracil are decreased. Recently, Stefanis et al.[26] in Greece administered chloramphenicol to 18 parkinson patients using a daily dose of 1.5 to 2.0 gm. orally for three to six weeks, and found improvement of the symptoms in all cases. In view of the action of chloramphenicol as a specific inhibitor of protein synthesis in the rapidly proliferating cells, they postulated an aberrant protein metabolism in the glial cells in parkinsonian brain.

Clinical Trial of L-DOPA

Small Dose

Brikmayer and Hornykiewicz,[27] in 1961, observed improvement in akinesia by slowly injecting 25 to 150 mg. of l-DOPA intravenously. The maximum effect was seen in two or three hours and persisted for 24 hours or longer. This was followed by several reports of beneficial effects of small intravenous injections in parkinsonism.[28,29,32,33] However, Fehling[30] in Sweden performed a double-blind study with low doses of l-DOPA and found no significant difference between l-DOPA and placebo. Rinne et al.[31] in Finland reported a questionable effect of this treatment in 1968. According to their strict double-blind study, improvement in rigidity or in daily activities was seen both in l-DOPA treated and in placebo-treated groups.

Large Dose

It was not until more recently that oral administration of larger doses was tried and found to be effective. McGeer and Zeldowics[47] in 1964 gave 1 to 5 gm. of dl-DOPA for several days to 10 patients with Parkinson's disease and demonstrated the presence of a dose-response relationship. Cotzias et al.,[41] in an extensive study reported in 1967, found improvement of parkinsonian manifestations in 50 percent of 16 patients administered dl-DOPA 3 to 16 gm. daily.

He and his associates recognized the necessity of giving large doses. However, they detected transient granulocytopenia of bone marrow in some patients receiving very large doses. They also found that l-DOPA was more effective than dl-DOPA, and the d-isomer caused blackening of urine, suggesting the inability of the d-isomer to be converted to dopamine in vivo.[57] This is why current trials have concentrated mostly on l-DOPA. The report of Yahr et al.[58] was based on the treatment and observation of 60 parkinsonian patients over a period of four to 12 months. They discontinued the conventional medications and used 3 to 8 gm. of l-DOPA with placebo studies in nine cases. Blind evaluation of clinical manifestations was performed daily by two evaluators who scored tremor, rigidity, akinesia, disturbance in gait and posture. Improvement was seen in 81 percent of the patients during the initial trial period of four to eight weeks, and in 91 percent during the follow-up trial period of four to 12 months. The first significant objective improvement appeared during the second week, at a dosage of 2.5 to 3.0 gm. per day. The important difference from the conventional anti-parkinsonian drugs is that the beneficial effect of l-DOPA is not only sustained for the period of observation, but there is some additional improvement on prolonged treatment. Withdrawal of l-DOPA by placebo substitution resulted in the gradual loss of the DOPA effect in the next several days. In this investigation, the beneficial effects of l-DOPA occurred regardless of cause, symptomatology or degree of severity of parkinsonism. Evaluation of the long-term effect of l-DOPA on each cardinal symptom of parkinsonism by a scoring system revealed that the average improvement was 72 percent in rigidity, 66 percent in tremor, and 57 percent in akinesia. The earliest beneficial effects were seen in rigidity and akinesia, and then later in tremor. Their data suggested that l-DOPA is 3½ times more effective than the anti-cholinergic drugs, but in some patients, a more satisfactory therapeutic result was obtained by combining l-DOPA with one of the anti-cholinergic agents.

Side Effects

The most common side reaction was nausea. Usually it occurred within the first few days of treatment, tended to appear shortly after an ingested dose, and lasted for 30 minutes to one hour. Multiple small doses and postprandial administration of l-DOPA reduced its intensity. Other side effects were vomiting, anorexia, postural hypotension, cardiac dysrhythmia such as paroxysmal tachycardia and premature ventricular contractions, and psychic manifestations such as agitation, insomnia and hallucinations. The most striking side effect was choreiform and athetotic movements which appeared on higher dosages and after prolonged administration, although they disappeared upon reduction of dosage. Laboratory abnormalities were rare, but included leukopenia and elevated BUN and SGOT. Barbeau[34] reported the favorable results in 79 percent of 80 patients, and stressed the importance of slow increase of dosage. The result of l-DOPA was also confirmed in double blind tests by Calne et al.[36,37] Now a number of reports of large oral doses seem to confirm the successful effects of this drug.[34-58]

Rationale for L-DOPA Treatment

In contrast with the conventional antiparkinsonian drugs which were used empirically, the therapeutic approach by l-DOPA was unique and important in that the trial was based on the close relationship between the neurochemical and neuropathological findings in parkinsonism. The pallor of the substantia nigra in parkinsonian brain is known to be due to decrease in the melanin pigment, which is one of the metabolites of tyrosine.[60] It is also known that reserpine sometimes produces extrapyramidal symptoms, probably by causing catecholamine depletion of the synapses. Based on these facts, the important investigations of

dopamine metabolism in the brain were made.

The rationale for this treatment consists of: (1) the presence of dopamine in the brain, localized chiefly in the striatum and substantia nigra, particularly in the synapses of corpus striatum,[59,62,63,64] (2) the subsequent discovery of its reduction in parkinsonism,[61,66] and (3) its depletion in laboratory animals following nigral lesions.[65,67,68]

Low Dopamine

Hornykiewicz[66] chemically analyzed 40 brains of patients with parkinsonism and found a strikingly low concentration of dopamine in the striatum and substantia nigra (Table). He also discovered the low concentration of homovanillic acid, a major breakdown product of dopamine, in the same brain areas of these patients. His group also found that large lesions in the substantia nigra produce more deficiency of dopamine in the caudate nucleus and putamen.[61] In addition, it was found that dopamine is decreased in these areas of the brain only contralaterally to the side of symptoms in a case of hemiparkinsonism. From these findings he speculated that in the brain of a patient with parkinsonism there is a reduced ability of the affected brain tissues to form dopamine or a disturbance of the storing mechanisms for dopamine in the striatum.

TABLE

Dopamine in the Healthy and Parkinsonian Brain[66]

	Caudate	Putamen	Subst. Nigra
Normal	3.5 μg/g	3.7	0.46
Parkinsonism	1.1	1.8	0 07

(Hornykiewicz, 1965)

Dopaminergic Fibers

By producing a unilateral lesion in the ventromedial tegmental area of the brain stem of 19 monkeys by electrocoagulation and by making pathological and chemical analysis of the brain one to nine months later, Poirier and Sourkes [67,68] in 1965 found a severe loss of cells in the pars compacta of the ipsilateral substantia nigra and low concentration of dopamine and of norepinephrine in the corresponding striatum. Fuxe and Anden[66] in 1965 demonstrated the same results by fluorescence histochemistry. Goldstein et al.[65] in 1966 also detected the fall of striatal amines after nigral lesions of monkeys and an impaired in vivo formation of dopamine-C^{14} from typrosine-C^{14}, suggesting a reduced activity of tyrosine hydroxylase. These facts suggest the presence of dopaminergic fibers from the substantia nigra projecting to the striatum.

Parkinson's Syndrome and Catecholamine Metabolism

The metabolic pathway of catecholamine is partly shown in Figure 5.[73] Since Cotè and Fahn[74] showed the presence of tyrosine hydroxylase[82] in the substantia nigra, neostriatum and globus pallidus of rhesus monkey in 1967, it is believed that tyrosine, transported to the brain, is converted to l-DOPA by this enzyme in the presence of reduced pteridine and copper. Then l-DOPA is decarboxylated to produce hydroxytyramine (dopamine) by DOPA decarboxylase,[77] which is also located in the synapses of those nuclei. Dopamine then is converted into norepinephrine and epinephrine, or is broken down to homovanillic acid through methylation and oxydative deamination. As far as these basal ganglia are concerned, the latter pathway seems to be the major pathway.[78,83,85,91] It is known that, among these three catecholamines, dopamine is the main substance which is abnormal in Parkinson's syndrome. In fact, dopamine is deficient in the basal ganglia of Parkinson's brain, and its final breakdown substance, homovanillic acid is known to be decreased in the spinal and ventricular cerebrospinal fluid

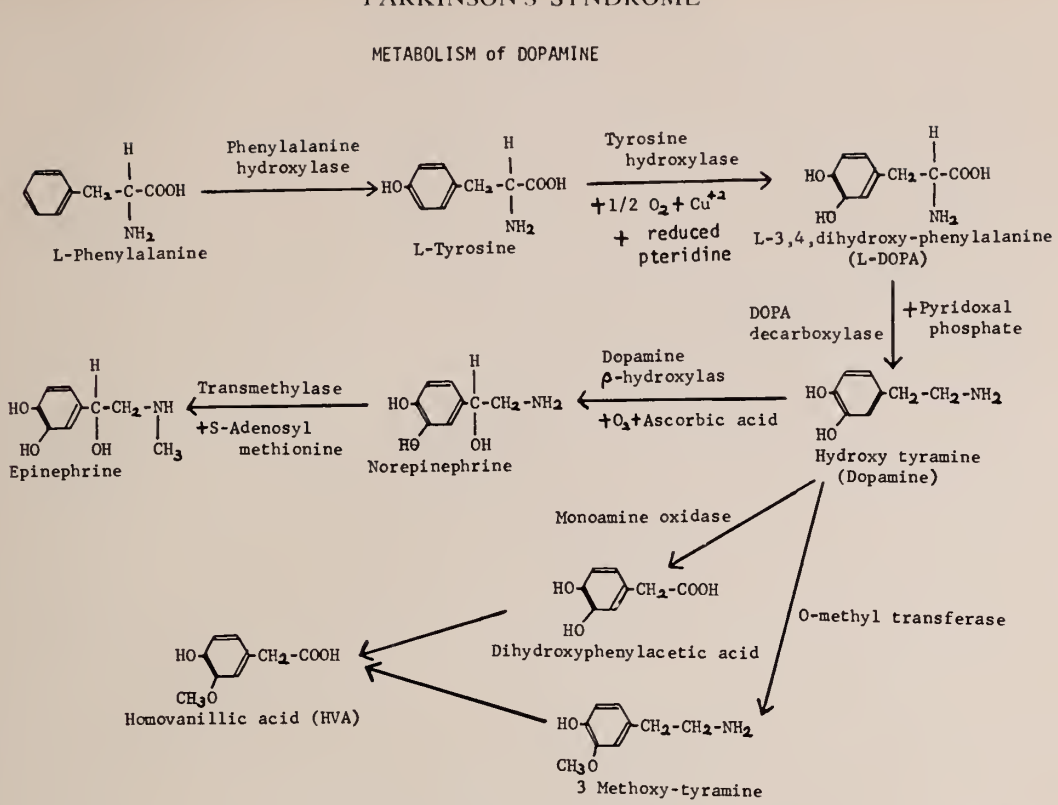


Fig. 5—Catecholamine metabolism.

(CSF) of the parkinsonian patients.[71,72,80,84,86] The rate-limiting steps of this pathway exist at the process of tyrosine hydroxylation. This is why administration of tyrosine per se does not improve parkinsonian symptoms.

The enzyme tyrosine hydroxylase is known to catalyze the hydroxylation of tryptophan as well as tyrosine in the presence of reduced pteridine and copper.[79,81] Likewise, DOPA decarboxylase is believed to be related with decarboxylation of 5-hydroxytryptophan to 5-hydroxytryptamine, serotonin (Figure 6). On the other hand, 5-hydroxyindole-acetic acid (5-HIAA), one of the final metabolites of the tryptophan metabolism, is reported to be decreased in the CSF of parkinsonian patients, suggesting disturbance of tryptophan metabolism.[72,80] When we take the impairment of these two metabolic systems into consideration, a

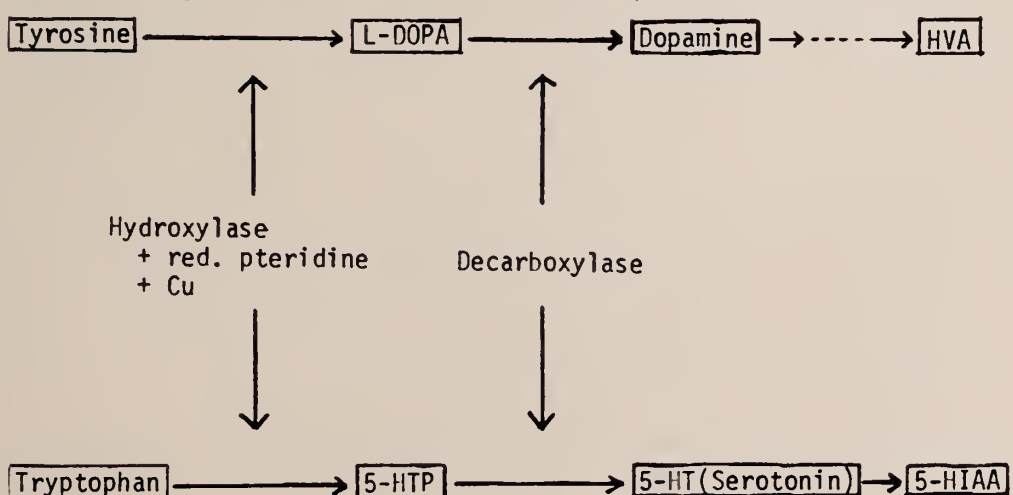


Fig. 6—Metabolism of tyrosine and tryptophan.

deficient state of this hydroxylating enzyme or the decarboxylase could be an important factor in the pathogenesis of Parkinson's syndrome. This probable abnormality of protein metabolism in parkinsonism in relation to abnormality of RNA metabolism appears to be the current subject of interest.

What happens to the ingested l-DOPA in the parkinsonsian patients? According to Tyce et al.[88] only less than 0.5 percent of the administered dose is detected in the plasma. Peaston and Bianchine[87] investigated its turnover by examining total serum radioactivity after giving C^{14}- labelled l-DOPA to the patients. As shown in Figure 7, l-DOPA, in the small (A) as well as large (B) dosage, is rapidly absorbed from the gastrointestinal tract to attain a peak level in the serum in an hour or two. Most of the dose is then excreted as metabolites in urine in eight hours. It may be concluded from this that frequent administration in divided doses is necessary to keep an adequate concentration in the blood. It is interesting to note here that the concentration of l-DOPA or its metabolites in the serum is lower after giving a therapeutic large dose (B) than after giving a smaller dose (A) of l-DOPA, probably because of the rate-limiting steps in the metabolic pathway in large doses. The blood level is even lower, when the same dose is given after a long-term l-DOPA administration (C). This is again probably due to the development of some rate-limiting steps during the course of treatment. L-DOPA is shown to penetrate the blood-brain barrier, whereas dopamine is not. After it reaches the brain parenchyma, particularly in the substantia nigra, striatum and globus pallidus, l-DOPA is converted to dopamine by DOPA decarboxylase. Subsequently, homovanillic acid, which is significantly lower in the CSF of the patients with parkinsonism prior to administration, increases above normal in the CSF,[76,84,89,90] indicating that the diseased striatum or substantia nigra is readily able to synthesize dopamine if presented with its immediate precursor DOPA. How l-DOPA is metabolized in the basal ganglia

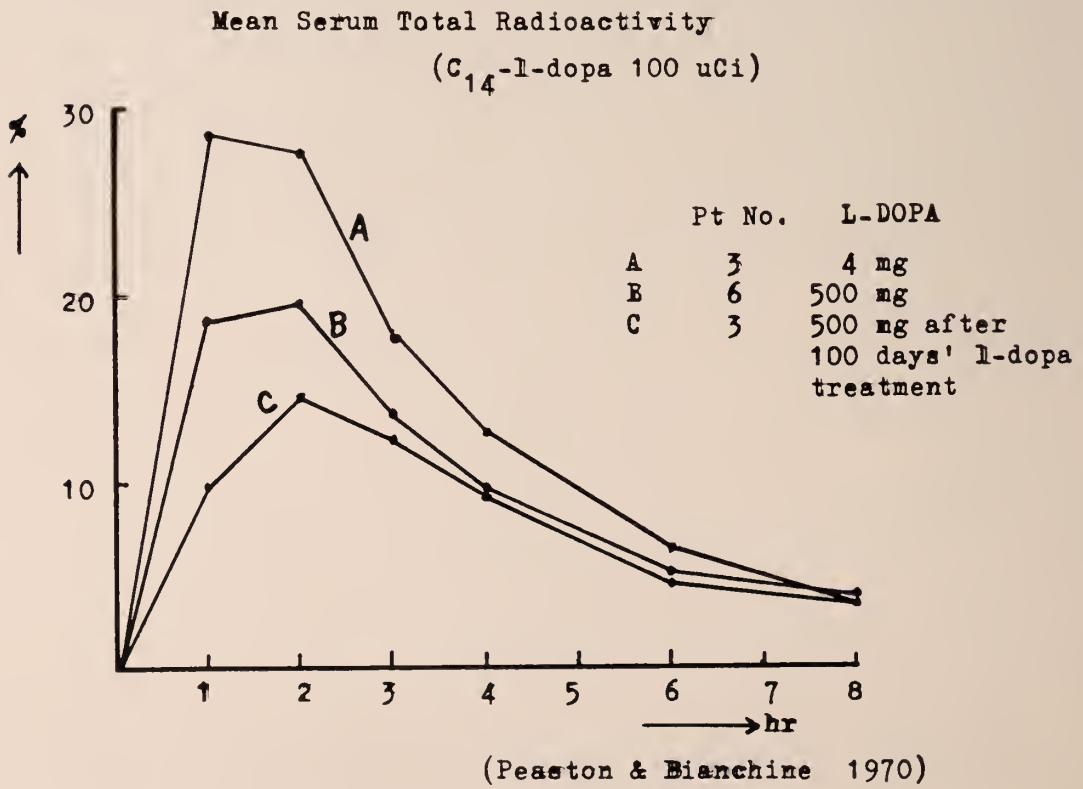


Fig. 7—Turnover of ingested l-DOPA.[87]

is not well known, but it is estimated from the various clinical facts and also from the experimental data of the peripheral sympathetic nerve terminals.[69] As shown in the schematic dopaminergic synapse (Figure 8), dopamine is synthesized and stored at the nerve terminal as a specific chemical transmitter, and liberated by the nerve impulse to work as a neurotransmitter. The liberated dopamine is supposed to be reabsorbed in the synaptic membrane and degradated by the action of monoamine oxidase. Reserpine, which may produce Parkinson's syndrome, causes depletion of dopamine from the synaptic terminals. On the other hand, phenothiazine is thought to block dopaminergic receptors, again producing Parkinson's syndrome. As already discussed above, trihexyphenidyl, diphenhydramine, imipramine, amphetamine and amantadine are supposed to inhibit the reuptake of dopamine into the synaptosomes, resulting in an increase of dopaminergic action.

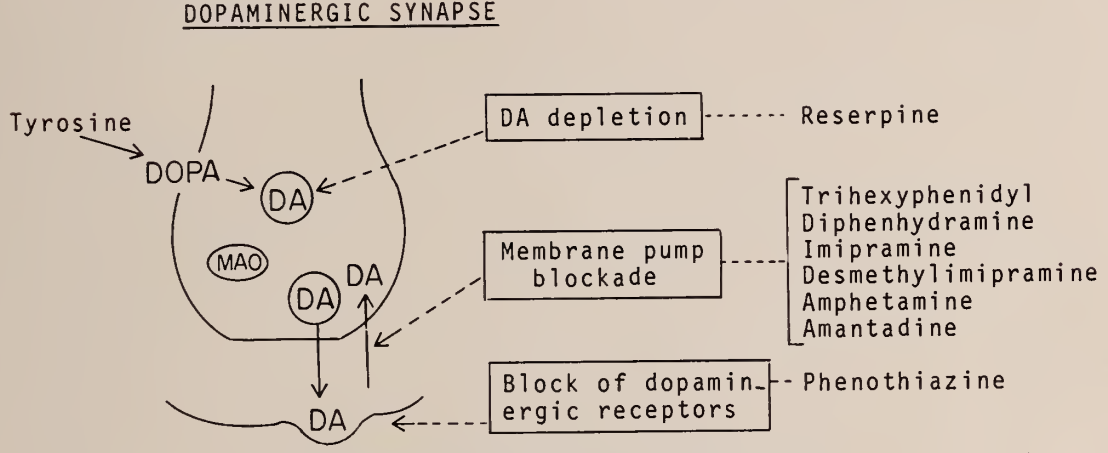


Fig. 8—Schematic illustration of dopaminergic synapse.

Pathophysiology of Parkinson's Syndrome

Dopamine not only is a precursor for norepinephrine and epinephrine in the brain, but also has a physiological role of its own. Bloom, Costa and Salmoiraghi[93] in 1965 examined the effect of acetylcholine, norepinephrine and dopamine on the discharge rate of caudate units of cats, and demonstrated that acetylcholine increased the discharge rate, norepinephrine reduced it moderately, and dopamine almost completely suppressed it. McLennan and York[95] also found that dopamine applied iontophoretically to caudate nucleus neurons inhibited the repetitive discharges induced by acetylcholine or by electrical stimulation. These data suggest that dopamine has an inhibitory effect on the caudate nucleus. Excitatory effect of cholinergic mechanism on the caudate nucleus was described in the section on atropine-like drugs.

In parkinsonism, there is now enough evidence to conclude that there is a defect of this dopaminergic modulation, resulting in overexcitation of the striatum. McGeer et al.[94] in 1961 proposed an imbalance between the cholinergic and dopaminergic systems as a pathophysiological basis of parkinsonism (Figure 9). Barbeau[92] in 1962 divided this system into the two (Figure 9). As for rigidity, the imbalance between acetylcholine and dopamine, and as for tremor, the imbalance between histamine and serotonin-norepinephrine were proposed to be important. When treating parkinsonian patients, it appears that atropine-like drugs antagonize the excitatory action of cholinergic system on the striatum, and dopamine accentuates the inhibitory action of dopaminergic system on the striatum, so that an appropriate balance can be attained between the two functional systems.

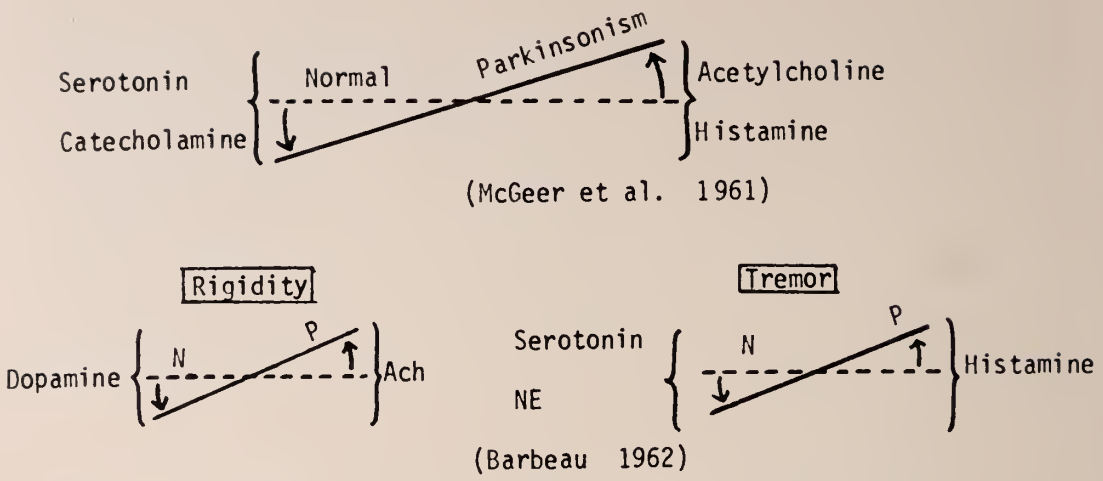


Fig. 9—Schematic illustration of pathophysiological basis of Parkinsonism.[92, 94]

Some Problems in L-DOPA Treatment

Although most of the side effects are controlled by regulation of dosage and by symptomatic therapy, the most disconcerting problem would be the development of abnormal involuntary movements. This is a kind of dyskinesia, but simulates none of the involuntary movements previously described. This is seen in the patients who have been on l-DOPA for a long period; according to Barbeau,[96] in 50 percent of 80 patients in general, in 60 percent of the patients with treatment for longer than six months, and in 73 percent of the patients for longer than one year. Barbeau[96] also observed loss or decrease of deep reflexes in all cases with this involuntary movement.

He injected various metabolites of 1-DOPA into rats intraperitoneally, and produced gnawing movements by l-DOPA and 3-methoxytyramine.[96] Decreased muscle tone in addition to gnawing was observed only in the rats injected with 3-methoxytyramine. He also noted the prominent effect of this substance in a group of rats which were given haloperidol in advance. Although the toxic theory is not well established, it is postulated that the previously existing lesion in the brainstem may give rise to hypersensitivity of catecholamine receptors to l-DOPA or one of its metabolites, producing the abnormal movements. As a matter of fact, long-term administration of l-DOPA in healthy people does not produce this involuntary movement,[34] which is very incapacitating and sometimes worse than Parkinson's syndrome itself.[96,98] This is reversible by reducing the dosage of l-DOPA,[58] but it must be reduced to a very low dose, where Parkinson's syndrome reappears. Pyridoxine was tried by Yahr's group and found to reduce this involuntary movement, but it was also noted that Parkinson's syndrome was aggravated by this. Jameson[99] reported a patient who had relief of the involuntary movement by intravenous injection of pyridoxine 10 mg., without aggravation of parkinsonism. The only way to prevent this side effect seems to be to increase the dosage of l-DOPA very gradually with small increments and careful titration of the dosage.

In order to decrease the therapeutic doses of l-DOPA and to maintain an equal blood level of l-DOPA, an agent to inhibit DOPA decarboxylase was used in 1967 by Birkmayer et al.[97] Barbeau[34,56] in 1969 reported a reduction in the daily l-DOPA dosage to 1 to 1.5 gm. from a level of 5 to 8 gm. by combining it with Ro 4-4602, which is an amino-hydrazine derivative that inhibits the decarboxylase and is believed to maintain high concentration of l-DOPA in the peripheral blood.

This approach seems to be very hopeful, if the side effects of Ro 4-4602 per se could be reduced.

Conclusion

Medical treatment of Parkinson's syndrome have been reviewed with particular reference to the mechanism of action, including conventional antiparkinsonian drugs, amantadine and finally l-DOPA. In relation to l-DOPA treatment, catecholamine and tryptophan metabolism in the basal ganglia, and the current hypothesis for the pathophysiology of parkinsonism have been discussed.

Acknowledgment: Dr. Milton Alter and Dr. David Webster kindly reviewed the manuscript.

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Complete list of references may be secured from the author.

Abstracts

A Traumatic Removal Of A Polyethylene Catheter From The Superior Vena Cava

A case reported in which polyethylene catheter was introduced via a metal needle through the left subclavian vein and was sheared and lodged in the superior vena cava. The use of a ureteric stone catching catheter proved an easy and effective way to retreat the fragmented catheter, thereby avoiding thoracotomy.

Josef Edelstein, M.D.

Chest 57: 4: 381, April 1970.

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Garland D. Perdue, M.D.; Robert B. Smith III, M.D.; Leeon Rhodes, M.D.; William D. Long, M.D.

Arch Surg 100: 5: 562, May 1970.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

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(Continued to Page 861)

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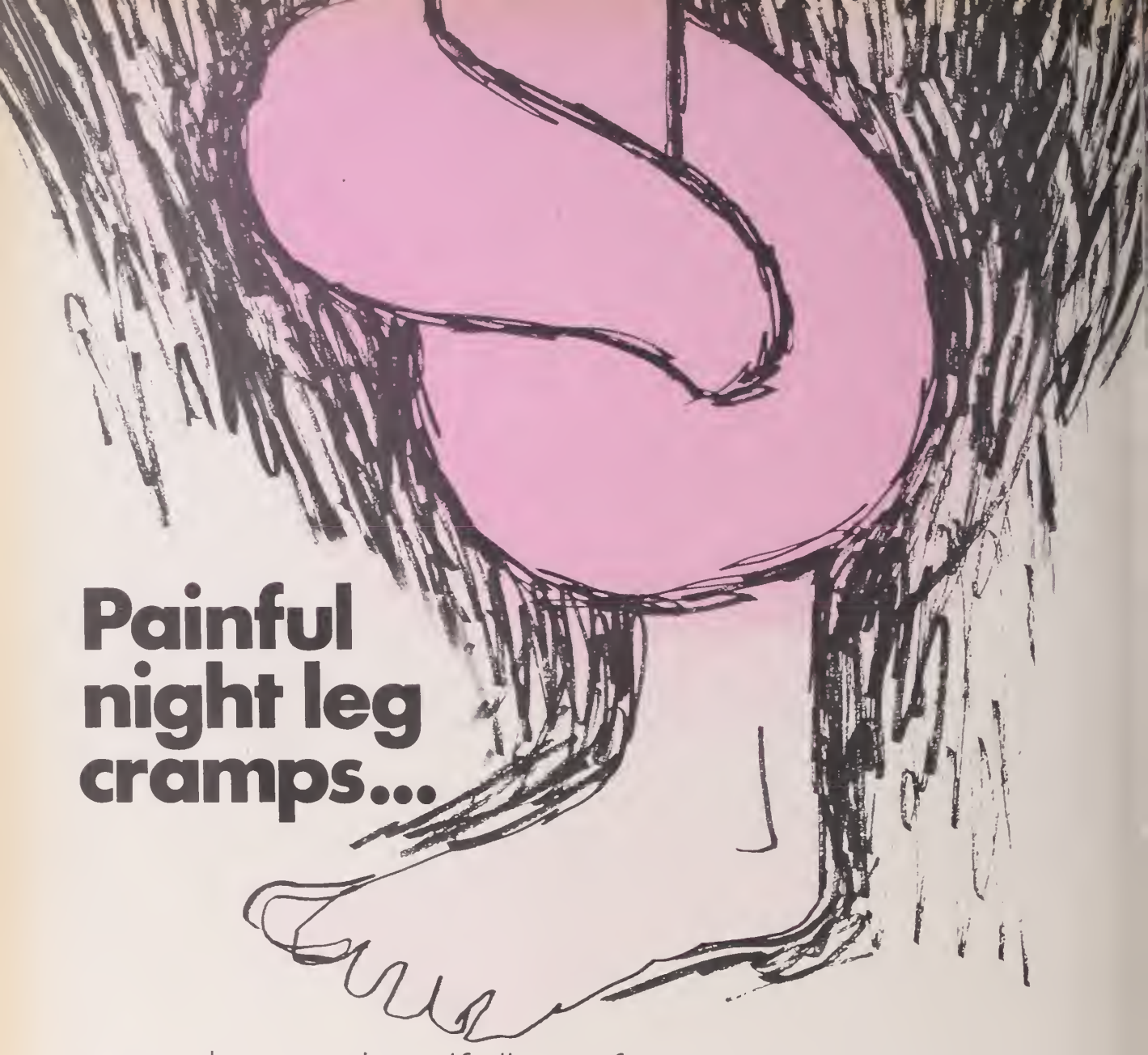
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History

History of the Treatment of Compound Fractures

RICHARD L. MULVANIA, M.D.* and JAMES E. JOHANSON, M.D.*

THAT INJURY WHICH probably most excites the young intern, the resident covering a trauma service, the experienced practitioner or the knowledgeable specialist is the compound fracture. Not that any one of them is likely to suffer a flogging ordered by Frederick The Great for an unsuccessful result in the case of a prize soldier, as Trueta says happened in eighteenth-century Prussia; but the problem has been an enigma that has only in recent decades achieved acceptable results. From the time of Hippocrates to the early years of World War I, the treatment of this condition was essentially that of the osteomyelitis which almost invariably resulted. The greatest progress in treatment has been made in war time, once again proving the wisdom of Hippocrates who said, "War is the only proper school for the surgeon."

Hippocrates

Many of the observations of Hippocrates (Figure 1) remain true today and, if his successors had followed his teachings properly, many centuries of mistakes in the treatment of compound fractures might have been avoided.

Healing Power of Nature

The most important feature of Hippocrates' teaching was the "healing power of nature." His basic concept of medical care was to aid nature in its work, and this was again pointed out in 1938 by Wangensteen who felt that the chief objective of a surgeon is to assist the natural defense mechanism of the body in overcoming or localizing infection. For compound fractures in which a "separation of bone" is not expected, Hippocrates suggests a "cerate mixed with pitch to be applied, a thin folded compress is to be bound upon it, and the parts around are to be anointed with white cerate." This "cerate" was most likely turpentine. Hippocrates goes on to state quite explicitly how the extremity should be bandaged with special care being taken to approximate the skin edges. He condemns a method, apparently prevalent during his time, of bandaging the involved extremity above and below the compound wound, apparently in order to apply cleansing medicine to the wound with more ease. He states that this manner of treatment will cause the wound to become swollen and discolored and the "lips everted, the discharge will be ichorous and

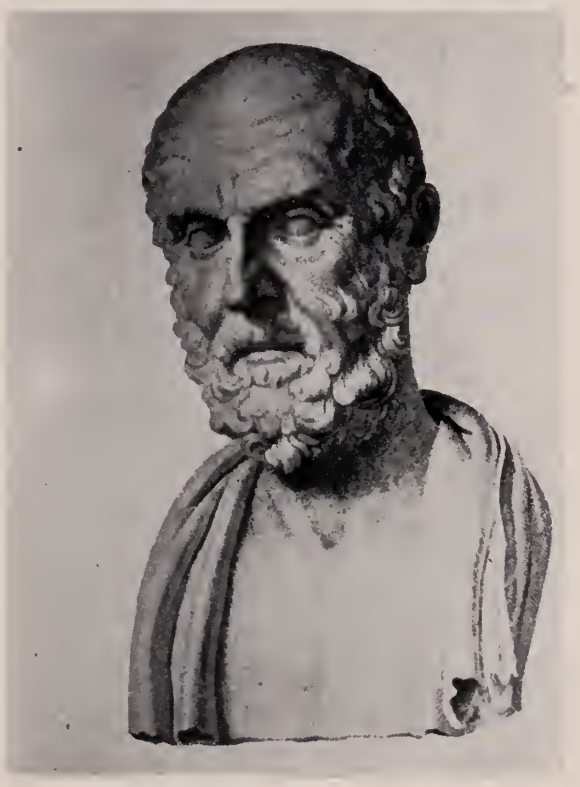


Fig. 1—Hippocrates (460 - 377 B.C.) His basic concept of the "healing power of nature" remains true today.

*Orthopedic and Fracture Divisions, Hennepin County General Hospital, Minneapolis, Minnesota.

without pus and the bones, which should not have gotten into a state of necrosis, exfoliate."

Hippocrates describes as favorable a separation of the wound with necrosis and sloughing of devitalized tissue, and he recommends that the wound be treated with compresses "dipped in a black austere wine."

Immobilization

Hippocrates further recommends that the extremity be treated in extension, being laid upon a "goat skin . . . spread below, so as to carry off the fluids which run from the wound." He states that in the summer season the compresses should be frequently dampened with wine, while in the winter they should be treated with greasy wool, moistened with wine and oil. Following the initial period of swelling, Hippocrates then recommends splinting the extremity until healing of the fracture occurs. He also suggests an alternative method for treatment of compound fractures, particularly of the tibia, variants of which have appeared in the literature for centuries. This method involves the use of "balls of Egyptian leather" placed about the leg below the knee and above the ankle and held in "distention" by four elastic rods, "made of the Cornel tree of equal length, and of the thickness of a finger." In this manner he suggests that the wound can be equally treated without disturbing the alignment of the fracture; however, he wisely adds that if any of the parts "do not fit properly, it does more harm than good." He adds a bit of advice, probably even more important in our age of mechanization, that "mechanical contrivances should either be properly done, or not be recoursed to at all, for it is a disgraceful and awkward thing to use mechanical means in an unmechanical way." In regard to the reduction of fractures, Hippocrates suggests the use of three iron levels in "those cases of fractures in which the bones protrude and can not be restored to their place." He mentions the great force necessary for reduction in this manner and mentions that the "lever along with extension, may be had recourse to on the day of the accident, or next day, but by no means on the third, fourth and the fifth."

Sequelae

He points out the danger of sepsis on these days but also adds the danger of convulsions, which might be construed to be what we today know as fat embolism, especially since he applies this warning particularly to fractures of the femur and humerus. He points out that, if convulsions should come on when reduction is effected, there is little hope of recovery." Reinforcing the present-day concepts regarding open reductions of the femur, in particular, he suggests that "when seven days have elapsed, or rather more, if there be no fever, and the wound be not inflamed, then there will be less to prevent an attempt at reduction."

Hippocrates' 87th aphorism, that diseases not curable by iron (the knife) are curable by fire, suggested the use of fire to cure infected wounds. It was not recognized that dead tissue was a danger and that cautery was harmful in that it destroyed tissue. The use of cautery persisted in the Arab School of Medicine for centuries as more true Hippocratic thought was rejected in favor of Galen's influence.

Galen

Although the teachings of Galen (Figure 2) were basically incorrect, his influence persisted



Fig. 2—Galen (131 - 201 A.D.) This early Roman's doctrine of "coction" persisted at least into the Renaissance in the treatment of wounds.

without question until the Renaissance, while many of his ideas have persisted even longer in a more refined form. In the healing of wounds, he viewed suppuration or, as he termed it, "coctio," as an essential part of the healing process. This "coctio" persisted even to the time of Lister as "laudable pus." Galen recommended "miraculous substances" to help this process by increasing "coction."

The School of Salerno

Theodoric (1205 - 1296) from the Medical School of Salerno (founded in the 10th Century as an adherent to Hippocratic teaching) opposed the Galen doctrine of "coction" and recommended "expectant" or dry treatment, suggesting, "it is not necessary that pus should be generated in wounds. No error can be greater than this. Such a practice is indeed to hinder nature, to prolong the disease and to prevent the conglutination and consolidation of the wound." *Henri de Mondeville,* a contemporary of Theodoric, felt that wounds of suppurative nature should be washed clean and left dry. However, his successor in the Montpellier School of Medicine which had been founded in the 8th Century, *Guy de Chauliac* (1300 - 1386), adhered to the Galenic doctrine of interference with the wound and spent years trying to find a "miraculous substance" that would produce suppuration and thus result in healing. Unfortunately, Guy de Chauliac's influence was greater than Theodoric's and de Mondeville's, and his principles spread throughout Europe and were the standard of practice until the Renaissance.



Fig. 3—Cauterization of Wounds. This form of wound treatment as suggested by Hippocrates' 87th aphorism persisted well into the Renaissance although rejected by Ambroise Paré in the 16th Century.

The Renaissance Area

Paracelsus

Paracelsus (1493 - 1541), in a book entitled "Der Grossen Wundärtzeny," published in 1528, noted that it was Nature's processes and not the surgeon's interference that heals wounds. Thus the teachings of Hippocrates once again came to the forefront. *Ambroise Paré* 4) was another adherent to the supreme healing power of nature who contributed greatly to the treatment of wounds. He rejected the use of cautery and boiling oil which was, at that time, popular in open-wound treatment and utilized only a nontoxic paste. Paré was eventually appointed the King's Premier Surgeon.

Brunnschweig

Brunnschweig, one of the most famous of the "Wundärzte," who were unqualified practitioners in the German-speaking areas more or less equivalent to the English "bonesetters," in his book "Buch der Wund-Arztney" (Strassburg - 1497) presents what is said to be the



Fig. 4—Ambroise Paré (1509-1590). He was an adherent of Hippocratic thought who rose in 15 years time from a poor barber-surgeon to the King's Premier Surgeon.

first detailed account of gunshot wounds, wherein he advocated the removal of free bone in osteomyelitis and compound fractures.

Botallo

Leonardo Botallo (born in 1530), in his book published in 1560, concluded that the infection of wounds was due to foreign bodies, in which category he included fragments of bone, contused and lacerated tissues, and clots of blood as well as foreign objects introduced from outside the body. Botallo suggested that these foreign bodies must be removed and the wound restored to as normal a condition as possible; however, his advice was largely ignored. A contemporary of Botallo was William Clowes (1540 - 1604), considered the best surgeon of Elizabethan England, who emphasized in his book, "Practice of Surgery," published in 1588, the necessity of removing all badly traumatized tissues.

Desault

Approximately two hundred years later these principles were re-established by Pierre Joseph Desault (1744 - 1795), who was the first to adopt "debridement," which he described as a deep incision to explore and drain a wound. Desault's student, Dominique Jean Larrey (Figure 5), is considered one of the greatest military surgeons of all times. At the age of 26 he was appointed Chief of the Medical Services of the French Army in the South, in which position he served under Napoleon. He adhered to Desault's principles of débridement in the treatment of compound wounds, but is probably more important for his contribution to the early treatment of wounds. He felt that the prognosis of compound injuries was to a large extent determined by the time interval from injury to surgical treatment. He developed the ambulance service which, although not original with him, has since been an important part of all armies and an essential part of the civilian treatment of compound fractures. A contemporary of Desault and Larrey was Neal who, in writing of his experiences in the American Revolutionary War, advised enlarging the surface of the wound to equal the depth of the wound.



Fig. 5—Dominique Jean Larrey (1766 - 1842). Treating the wounded during Napoleon's Egyptian campaign of 1798 - 99.

The Turn of the Century

Louis Ollier

Louis Ollier (1825 - 1900), during the Franco-Prussian War, devised a technique of completely immobilizing a limb afflicted with a compound fracture, utilizing a plaster of paris cast, a technique described by Mathijsen in 1852. This technique he called "occlusive technique," since he believed that absolute rest facilitated wound healing. He did not apply this technique to recent severe injuries since by this time the "débridement" of Desault and Larrey had been long forgotten. So also were Ollier's principles, but, as is so often the case, they were to emerge fifty years later as the Orr method.

Lister

In a series of articles appearing in *Lancet* in 1867, Joseph Lister (Figure 6) introduced antisepsis in the treatment of wounds. He felt that the infection or the suppuration of a compound fracture was secondary to decomposition of the blood and tissues due to "access of the atmosphere." He felt that the coagulum at the orifice of a wound, when allowed to form a crust or scab, adverted the consequences of a compound fracture since the air was excluded. He credited Pasteur's germ theory as the element in the air responsible for suppuration. Lister chose carbolic acid as his principal antiseptic compound, noting the "remarkable effects produced by carbolic acid upon the sewage of the town of Carlisle." His first attempt at clinical investigation was in March of 1865 and was deemed unsuccessful because of, as he says, "improper management." In a second attempt on August 12,

1865, he used carbolic acid on an eleven-year-old boy with a compound fracture of the left leg. He placed lint soaked in carbolic acid into the wound, splinted the leg with pasteboard and then dressed the wound with carbolic acid for five days. The treatment was successful. Unfortunately, Lister's introduction of antisepsis did not have the effect it should have had in the treatment of compound fractures. As his technique became generally accepted, the Galenic attitude toward a "miraculous substance" reappeared, surgical debridement was forgotten, and surgical technique was reduced to a mere attempt at killing bacteria through antisepsis.

Reyher - Dennis

This was doubly unfortunate since at the 7th International Surgical Conference in 1881 Reyher was able to definitely establish the importance of the time factor in debridement. He showed that when immediate wound excision and antiseptic treatment were employed, the mortality rate was reduced from 53.7% to 23.6%. In 1894 Frederic S. Dennis of New York likewise applied sound principles of compound fracture care, very similar to those to be later employed by Trueta, to treat one hundred cases without a death from any cause. The abandonment of time-honored principles of wound care in favor of the search for a better antiseptic prevailed until World War I when the ravages of war retaught old lessons. With all due credit to Lister's antisepsis, however, it must be pointed out that asepsis gradually supplanted antiseptic technique as a consequence of the discoveries of Pasteur and Semmelweis.



Fig. 6—Joseph Lister (1827-1912). Introduced antisepsis in the treatment of wounds in 1867.

Modern Day

In the initial phases of the "Great War" beginning in 1914, it was felt that wounds produced by bullets were of little significance and thus debridement was considered of little value. Infection rates soon proved this wrong and debridement once again came into use. Pierre Duvall carried this to the extent that during the battles in Flanders he closed wounds primarily after excision of all dead and dying tissues within the first six to eight hours.

Carrel - Dakin

The search for a proper antiseptic included the investigation of perchloride of mercury, alcohol, ether, and carbolic acid before the Carrel-Dakin technique was settled upon. In 1915, at the Academie de Medecine in Paris, Carrel reported that antiseptics were valuable in the treatment of wounds when used properly; he quoted Tuffier's statement that of 1,000 amputations at Maison Blanche, 800 had to be done because of complicating infection. Carrel suggested that this was due to a poorly formulated treatment regimen and further suggested that this was not necessary if treatment was done properly according to his principles. Essentially Carrel's technique employed the use of Dakin's solution, a very carefully prepared solution of sodium hypochlorite with high germicidal action and minimal tissue reaction, to irrigate the wounds. The solution was introduced into all recesses of the wound by as many tubes as necessary every two hours during the day and two or three times during the night. Sodium hypochlorite was the essential agent Semmelweis utilized in 1847 for hand washing and instrument sterilization.

Winnett Orr Debridement

As the First World War ended, it became apparent that there were several disadvantages of the Carrel-Dakin method of treatment of compound fractures. These were pointed out primarily by Winnett Orr of Lincoln, Nebraska, while a member of the medical corps of the American Expeditionary Forces in France. Among the disadvantages were the technical problems themselves requiring special training, the danger of secondary infection, the near to continuous care, and the necessity for daily dressing changes as well as, most importantly, the necessity of ignoring the fundamental orthopedic principles of immobilization in a correction position in order to allow healing to occur. With undue emphasis placed on frequent dressing changes, the "bone injury or the joint lesion was often being allowed to drift into deformity while a relatively unimportant soft part wound was being given daily so-called antiseptic dressing of no particular value." These conclusions he based on the finding that of 1,000 orthopedic patients arriving in Savenay apparently ready for evacuation to the United States, 500 required a change of splints while one fourth to one third required surgery to effect drainage or a shift in the position of the bony fragments. Thus Orr was influenced in his conclusions following the war in the harmfulness of frequent dressing changes for compound fractures and summarized his method of "drainage and rest" as follows:

1. Immobilize patient in best position on operating table.
2. Give a thorough debridement or drainage operation.
3. Pack entire wound open with vaseline gauze, using no suture or drainage tubes.
4. Apply extensive well-fitting plaster of paris cast.
5. Do not disturb the wound or part except for definite complications.

In this manner he treated quite successfully many cases in his private practice with as few as three or four dressing changes.

Orr's treatment, which became known as the "closed plaster technique," was successfully utilized and advanced by Trueta during the Spanish Civil War in the treatment of 20,000 cases of compound fracture. This technique was so successfully employed that, as Trueta says, "The incidence of gas gangrene and of other infections fell so markedly that it has been suggested that the soil of Spain contains no anaerobes." Trueta recommended keeping the cast for approximately 10 to 15 days in the summer and for about a month in the winter.

Maggot Treatment

An additional observation made in World War I, which was for a time a useful adjunct to the treatment of compound fractures, was made by Baer. In an article published in 1931 he reports that in 1917 he found two soldiers with compound femoral fractures who were bypassed for seven days on the field. When they were found they displayed no evidence of septicemia although they had had no care whatsoever. On inspecting their wounds, it was seen that they were teeming with maggots from the blow fly; when the wounds were cleansed, it was noted that they were "filled with the most beautiful pink granulation tissue that one could imagine." Cultures of the wounds revealed only a few staphylococci and streptococci, insufficient for pus formation. With treatment, the wounds healed without difficulty. This stimulated clinical use of maggots for chronic osteomyelitis. Baer used sterile maggots which he cultured for the treatment of 89 cases. In a review of the literature, Goldstein revealed that Ambroise Paré, Fabricius, Zackman, Larrey, Shafer, Crile, and Keen observed and reported favorable results in wounds infected with maggots; but until Baer no deliberate use of maggots had been reported.

Sulfa Drugs

With the introduction of the sulfa compounds, antiseptics and maggots became less important. Jensen, Johnsrud, and Nelson introduced sulfanilamide to the treatment of compound fractures in 1939 at the Minneapolis General Hospital; they treated 39 compound fractures and two compound dislocations with local crystalin and sulfanilamide. Their infection rate was less than 5% only because they reported two fractures recompounding and becoming infected. This was compared to 94 open fractures treated by similar

methods except that no sulfanilamide was used. These 94 cases showed an infection rate of 27%.

In 1941, Key indicated that in civilian practice most compound fractures could be sutured primarily after thorough debridement and the use of sulfanilamide powder if the wounds were treated early, that is, within six to 12 hours and if they were not markedly damaged or contaminated. He did not feel that oral sulfanilamide was necessary unless there were special circumstances such as a more contaminated wound or a longer time interval after injury. He did recommend, however, that the more severe civilian injuries and war wounds should be left open, and he further recommended the use of oral sulfanilamide in these cases. In this early report, Key felt that internal fixation was possible with the use of sulfanilamides.

In the same year, Campbell and Smith reported 143 cases treated with sulfanilamides, of which 42 were subjected to internal fixation. In the treatment of compound fractures, they recommended the care of the systemic problems, debridement of the wound, and irrigation with four to five liters of saline solution. They utilized sulfanilamide crystals locally and oral sulfathiazole, and it was their contention that metallic internal fixation could be "applied without hesitancy if it is indicated." They showed a reduction of the infection rate from 33.3% to 18.1% in cases where primary internal fixation was used.

In 1946, Key reported on the use of penicillin and sulfathiazole in the treatment of chronic osteomyelitis, indicating that these drugs were valuable adjuncts to the surgical approach, which he outlined as complete removal of sequestra and of dead and infected bone and obliteration of dead space.

With the onset of the Second World War, further lessons about management of compound fractures had to be learned. The glowing reports of primary closure of compound fractures in civilian practice led to an attempt at primary closure in the early phases of the war; however, as Hampton states, "The wartime experience with primary closure of soft tissue wounds was brief and unhappy." In the initial period of the North African Campaign, wounds were debrided in a forward hospital, dressed with vaseline, and placed in plaster with the fractures reduced. The extremity was kept in plaster for four to six weeks under the assumption that the wound was healing by granulation. However, it soon became apparent that pressure sores, skin excoriations, and pin-tract infections could develop as well as loss of fracture reduction during this interval.

Delayed Closure

Cleveland and Grove, MacFarlane, and Hampton reported the efficacy of delayed primary closure of wounds. MacFarlane further reported that the use of sulfanilamides did not seem to increase healing or lessen infection when used locally, but that oral usage might cut down the evidence of severe infection. In a report on 2,393 patients, Cleveland and Grove found that 87% of the wounds were converted from compound to simple fractures by delayed primary closure; they attributed their success to early and adequate surgical debridement, rapid evacuation to rear medical installations, good surgical technique, penicillin and sulfa drugs, and blood transfusions. The principle of delayed primary closure as reported by Hampton included aggressive debridement of dead and devitalized tissues with elimination of dead spaces. In Hampton's experience, "No loss of life or limb could be attributed to this aggressive surgery." He felt that the best evidence of adequate initial surgery was a clinically clear wound five days later and that an unreduced fracture in the presence of an unhealed wound need not be accepted.

In the Mediterranean Theater of Operations, Hampton reported 332 cases of delayed internal rigid fixation of compound fractures using plates, screws, or cerclage wires. These procedures were performed five to 10 days following the initial injury and were designed to prevent or cut short infection and to promote healing of the wound. His objectives were to minimize sepsis, to reduce the fracture maximally, to heal the wound as fully as possible with minimal scarring, and to restore function of the extremity to a maximum. He reported that 77% had a maximal achievable result and concluded that there was a "place for the delayed internal fixation of battle fractures."

Contemporary

In 1945 Knight and Wood, and Kelly, Rosati, and Murray presented papers regarding the reconstructive phase of compound fracture treatment. Knight and Wood considered bone cavities associated with skin and soft tissue defects among the most serious problems. They suggested, first adequate sequestrectomy, next application of a splint and a skin graft, and then excision of the initial skin graft with application of bone grafts and coverage with full thickness skin as a reasonable approach to this problem. Kelly, Rosati, and Murray suggested saucerization of wounds by secondary debridement and then use of the Orr dressing technique. They substituted fine mesh gauze for vaseline gauze in order to obtain a smooth granulating bed. Eventually they supplied coverage with local and pedicle flaps.

Under civilian conditions, Gustilo et al. have shown in an analysis of cases treated at Hennepin County General Hospital from 1955 to 1966 that primary closure of compound wounds is possible; however, they recommend that when there is doubt that an adequate debridement of contaminated tissue be done, the wound should be left open, and treated with secondary or delayed closure. Following the principles to be summarized, they report, in the last five years of their study, an infection rate of 4.14%. Their recommendations are as follows:

1. Transfer of patient to operating room as soon as possible.
2. Complete debridement of contaminated tissues with copious irrigations of wounds.
3. Massive intravenous administration of antibiotics.
4. Primary closure when possible with secondary or delayed closure if there is doubt as to the adequacy of debridement.
5. Avoidance of primary metallic fixation.
6. Adequate treatment of infection.
7. A team approach to multiple injuries.

We have now reached a stage in the treatment of compound fractures where there are fairly definite guidelines with excellent results obtainable. There are still some areas of disagreement, however: specifically, the question of primary metallic fixation and primary versus delayed primary closure. Thus far, the advancement of knowledge in the treatment of compound fractures has been marked by multiple instances of disregard for solid principles established by sound-thinking predecessors. This phenomenon dates from the rejection of Hippocrates' "healing power of nature" in favor of the pursuit of a "miraculous substance." One should not allow "coctio" of the mind to obscure the fertility of thought which progresses without disregard for the wisdom of the past.

Acknowledgment

The authors wish to acknowledge the help and contributions by Owen H. Wangensteen, M.D., Ph.D., in the preparation of this paper.

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Deja vecu—an illusory feeling of having previously experienced something—from French "already lived."

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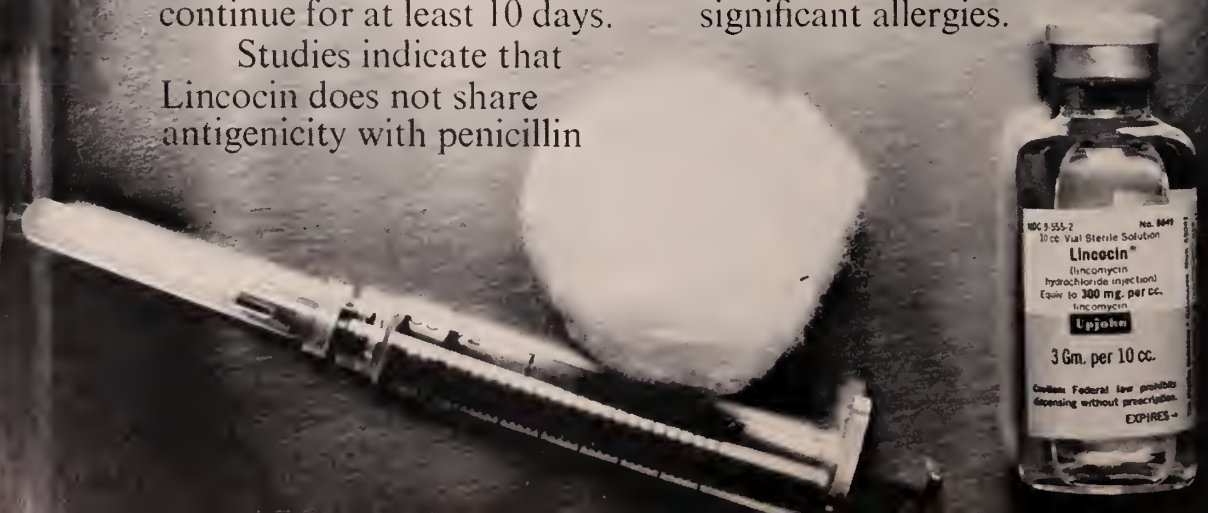
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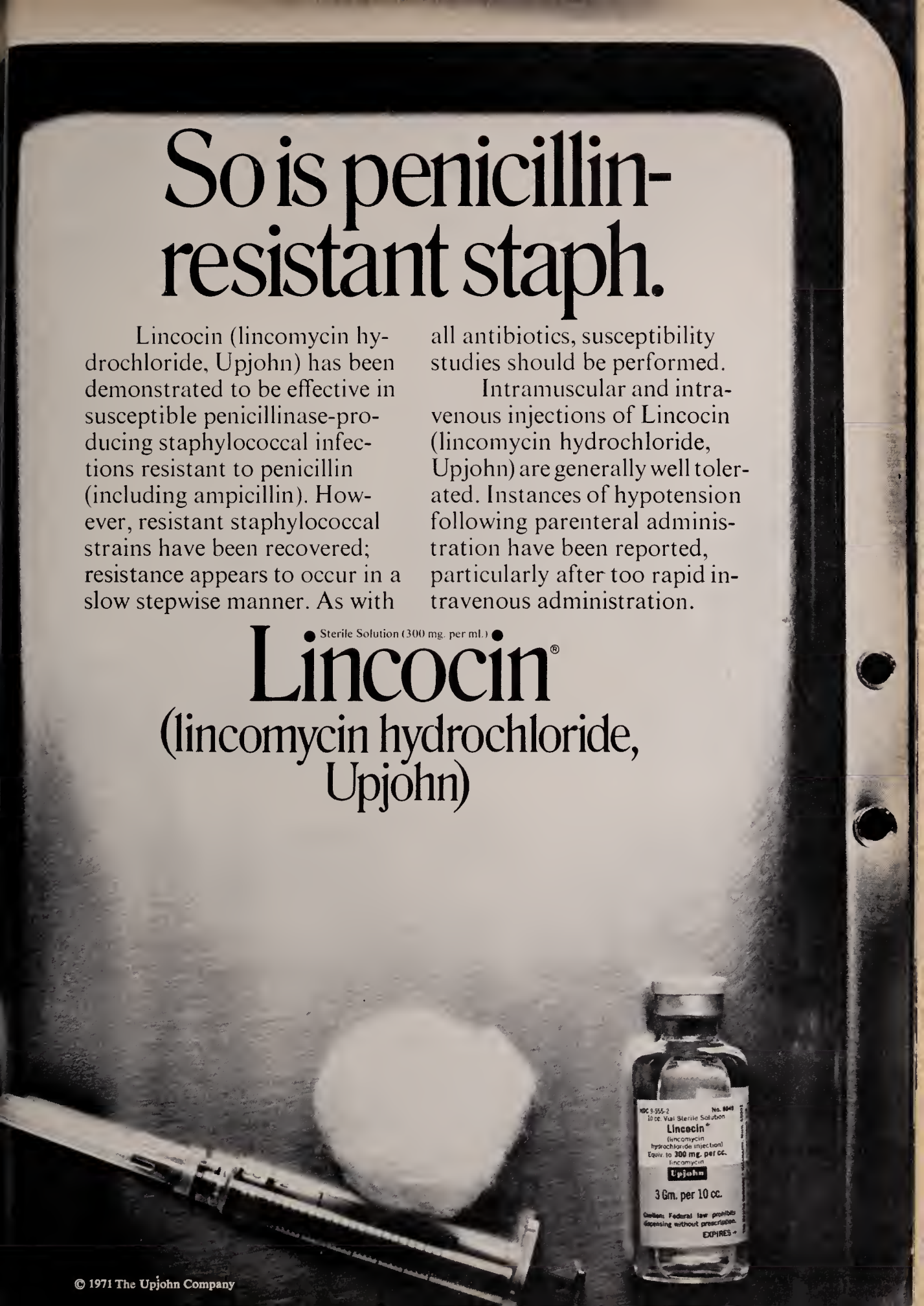
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Book Reviews

A book that is shut is but a block—Thomas Fuller.

FUNCTIONAL ANATOMY OF THE LIMBS AND BACK; Hollinshead; W. B. Saunders Co.; 420 pages, 170 figures; $12.50.

This is a beautifully illustrated monograph on the functional anatomy of the limbs and back, with a great deal of useful clinical application to the industrial surgeon and the physiatrist. All of the illustrations are ink drawings, clear, concise, and to the point. Minute details of anatomy are not included but are not necessary.

I can sincerely recommend this book to any physician who has interest in anatomical function as well as physiologic and neurologic function.

C. O. Rice, M.D.
Minneapolis, Minnesota

INTRODUCTION TO MEDICAL DECISION MAKING. Lee B. Lusted, M.D. Charles C Thomas, Publisher, Springfield, Illinois, 1968, 271 pages.

This is a leading textbook on the use of Bayesian Statistical Analysis with or without computer in medical diagnosis and similar decision problems. A pioneering effort in this rapidly growing field, it has already attracted wide attention not only among medical men but also by statisticians, operations researchers, and management scientists dealing with decision problems involving risk in quite different areas but using essentially similar mathematical tools. This book is indeed a model of its kind. Written by a distinguished authority, it is lucid, forthright and to the point. While making no concessions to rigor it is written in such a logical manner as to be intelligible to every person with scientific training. The mathematical techniques are kept to the barest minimum and the emphasis is throughout on the logic of reasoning.

The book begins with an exposition of the fundamental ideas of personal probability, likelihood and Bayes principle. These are then applied to medical diagnosis using actual data on such cases as thyroid disease, congenital heart disease, and primary bone tumors. The clinician may well want to read this chapter first before diving into the statistical theory underlying the procedure. The method is further elucidated through the use of decision trees and flow charts, two indispensable tools of modern decision theory (Chapter 3). Chapter 4 deals with the thorny problems of observer error; Chapter 5 leads right up to the frontier of knowledge, introducing the subtle concept of utility and dealing with problems of treatment decisions, and suggestions for research and development.

An extensive bibliography and detailed appendices presenting flow diagrams and ready-made computer programs greatly enhance the value of the book as a teaching device. It is to be wished that the important and far-reaching ideas developed in this book will find wide and rapid acceptance in the practicing medical profession.

Martin Beckmann, Ph.D.
Brown University

CURRENT DIAGNOSIS AND TREATMENT, Brainerd, Knapp, Chalton, and Margen, Lange Medical Publications, Los Altos, California, 1970; 884 pages.

Every doctor's office requires a ready source of reference for diagnosis and treatment. This book is intended to serve the practicing physician and, no matter what his specialty, he may find need for reference to diseases that he would not himself be attending. The clinical findings, differential diagnoses, complications, treatment and prognosis are provided in brief for a very extensive list of diseases: medical, gynecological, orthopedic, vascular, genitourinary and nervous diseases. For the physician who may wish to obtain reference to a host of diseases for whatever reason this book is well worth the price.

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LIVER BIOPSY INTERPRETATION. Peter J. Scheuer, M.D. Senior Lecturer in Morbid Anatomy Royal Free Hospital, School of Medicine, University of London. The Williams and Wilkins Company, Baltimore, 1968. Pages 138. Color plates 13. Black and White figures 89. Price $15.50.

This book is written for the clinician and pathologist who wishes to perfect himself in the art of interpreting needle liver biopsies. Described and illustrated are architectural changes in such conditions as biliary obstruction; toxic, alcohol, drug-induced, viral hepatitis; cirrhosis; benign and malignant neoplasms; vascular diseases; glycogenesis; siderosis; hemochromatosis; and infective and parasitic diseases. Hematoxylin-Eosin stained paraffin sections 3-5 micra in thickness comprise the greater number of illustrations. Preparing of cryostat frozen sections is briefly presented. Electron microscopy of a normal liver cell and processing of liver biopsy tissue for electron microscopy are given concise accounts.

The black and white figures are clean and sharp; the plates are exceptionally well balanced, and the color reproduction is excellent. This allows the reader to readily assess the architectural changes.

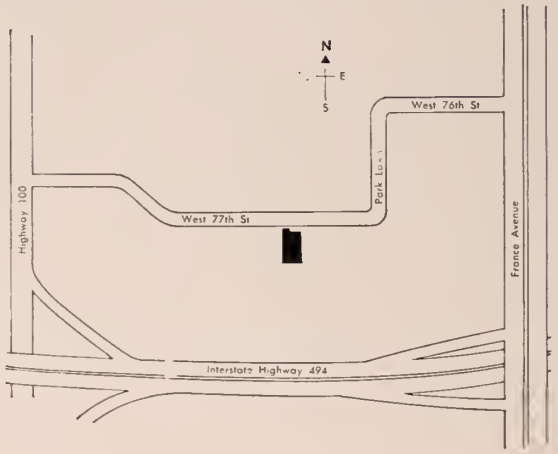
Though Dr. Scheuer states that ". . . no attempt was made to describe the whole field of liver pathology" I concur with Dr. Sherlock who wrote the book's foreword that ". . . pathologists faced with a decision on the histological appearances of a liver biopsy will be glad to have this book at their elbow."

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Usage In Children Not recommended for use in children under 12 years of age.

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Central Nervous System: When CNS side effects occur, they are most often manifested as drowsiness or sedation or overstimulation and restlessness. Insomnia, dizziness, headache, euphoria, dysphoria, and tremor may also occur. Psychotic episodes, although rare, have been noted even at recommended doses. **Cardiovascular:** tachycardia, palpitation, elevation of blood pressure. **Gastrointestinal:** nausea and vomiting, diarrhea, unpleasant taste, constipation. **Endocrine:** changes in libido, impotence. **Autonomic:** dryness of mouth, sweating, mydriasis. **Allergic:** urticaria. **Genitourinary:** diuresis and, rarely, difficulty in initiating micturition. **Others:** Paresthesias, sural spasms.

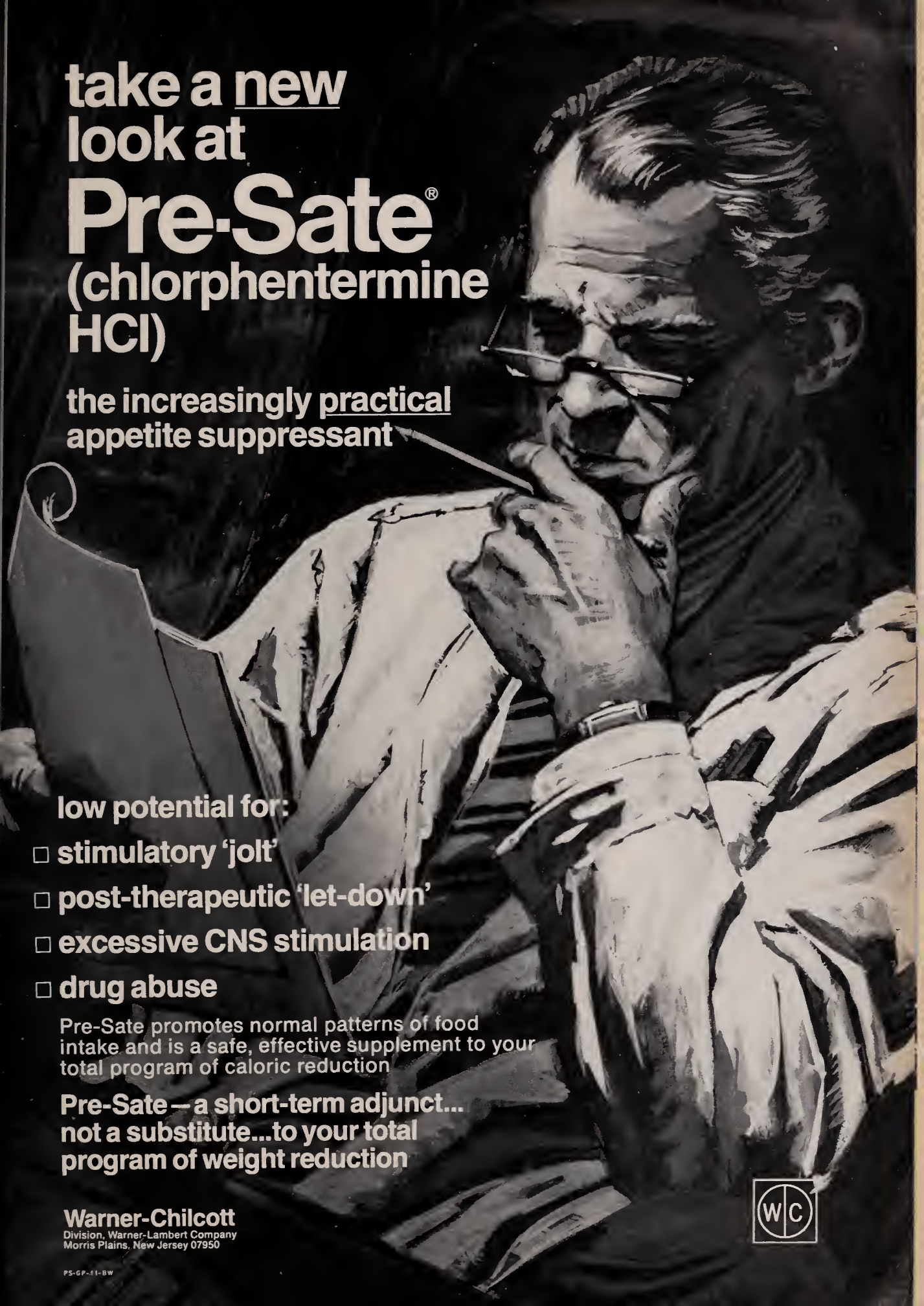
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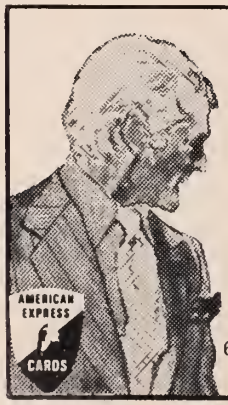
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Dalmane (flurazepam HCl) 30 mg reduced awake time—both before and after falling asleep - by fifty percent of pretreatment values in patients with insomnia.[1,2]

Two sleep laboratory studies recently confirmed findings of earlier studies of this type, namely, that Dalmane 30 mg was effective in patients who had trouble falling asleep, staying asleep or both. One 30-mg capsule of Dalmane usually induced sleep within 22 minutes, decreased the number of awakenings and the wake time after the onset of sleep, and provided 7 to 8 hours of sleep without need to repeat dosage during the night.

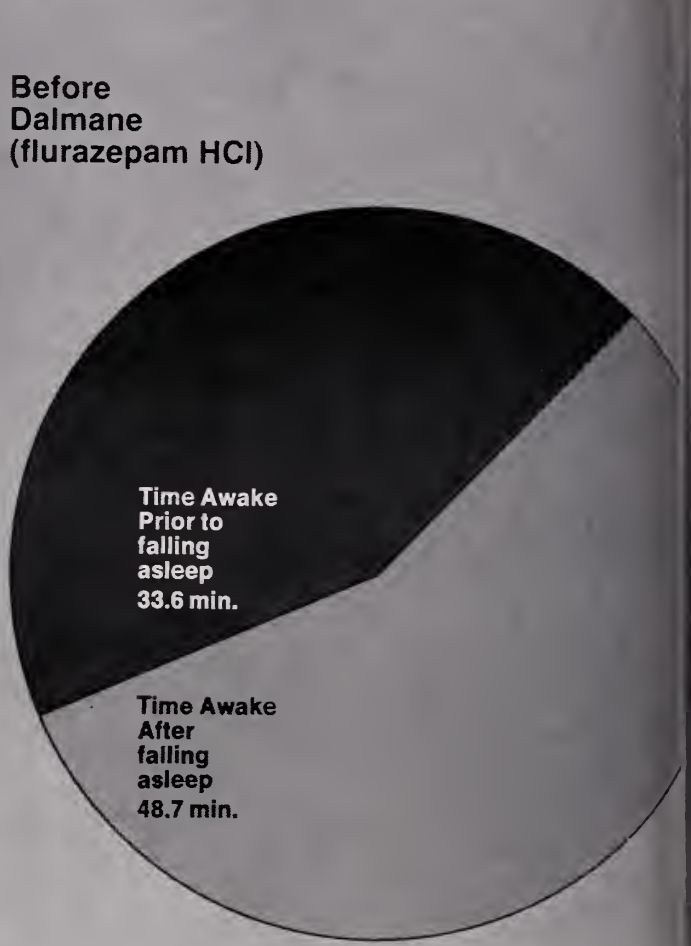
These studies utilized identical protocols and included eight insomniac patients. Sleep laboratory measurements in a limited number of patients are derived from all-night electro-encephalographic, electro-oculographic and electromyographic tracings. Unlike traditional methods of evaluation, they are quantitative, reproducible and projectable to large numbers of subjects.

Results shown represent average values in all subjects for the three consecutive nights of placebo administration prior to Dalmane therapy and the seven consecutive nights on Dalmane 30 mg.

Dalmane is also relatively safe, as reported in clinical studies. Instances of morning "hang-over" have been relatively infrequent; paradoxical reactions (excitement) and hypotension have been rare. Dizziness, drowsiness, lightheadedness and the like were the side effects noted most frequently, particularly in the elderly or debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

References: 1. Frost, J. D., Jr.: "A System for Automatically Analyzing Sleep," Scientific Exhibit presented at Clinical Convention, A.M.A., Boston, Nov. 29-Dec. 2, 1970, and Aerospace M.A., Houston, April 26-29, 1971.
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley, N.J.

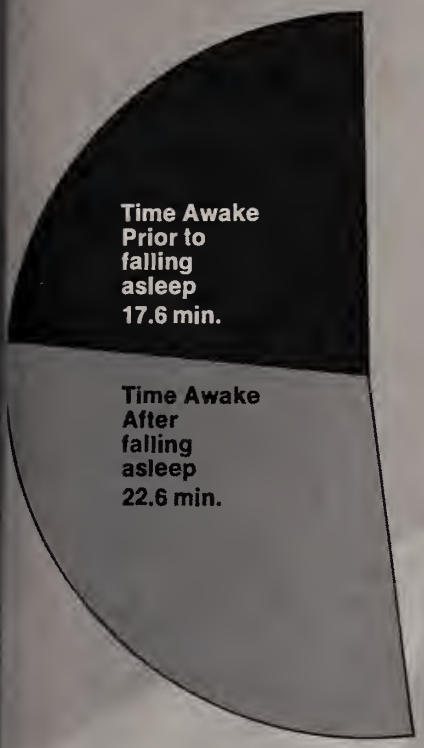
Before Dalmane (flurazepam HCl)



Measurements of sleep in the sleep laboratory are obtained with electroencephalographic, electro-oculographic and electromyographic recordings.

nd slept through the night

On
Dalmane
flurazepam HCl)



ge sleep laboratory measurements in cited studies

neter	Before Dalmane	On Dalmane
required to fall asleep	33.6 min.	17.6 min.
time after onset of sleep	48.7 min.	22.6 min.
ber of wakeful periods after set of sleep	12.2	8.4
sleep time	420.0 min.	447.5 min.
sleep percent	88.6	94.5

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

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President's Letter



Minnesota Thoracic Society

DR. J. ARTHUR MYERS, in the Preface to his, historical masterpiece, *Invited and Conquered,* writes of those persons who, over the years, fought the White Plague: "It is doubtful whether in the world's history such a group of resolute, courageous, competent, well-informed, sincere, and hardworking men and women ever participated in the solution of such a serious tuberculosis problem on a state or provincial-wide basis. Certainly no group ever exceeded and few have equalled their accomplishments." And in another place, Dr. Myers points out: "Throughout this volume one finds debate and even bitter controversy over some subjects. This has characterized the medical profession since its beginnings and greatly safeguarded the public. Everyone who has expressed a new thought, developed a new procedure or made a discovery has been challenged, not always by disbelievers, but by those who demanded further evidence and confirmation. Debate and controversy stimulate thought, which leads to greater activity, and ultimately, truth prevails."

These two ideas reflect admirably the concept of the Minnesota Thoracic Society since its founding. The purpose of the Society, as stated in its Constitution, has been "the stimulation of the scientific study of pulmonary and intrathoracic diseases and closely allied subjects." The Society was first organized in the fall of 1925 under the name, Minnesota Trudeau Medical Society. This was 14 years before the American Trudeau Society and its component state organizations were formed. In 1960 the name was changed to the Minnesota Thoracic Society when the national organization changed its name to the American Thoracic Society.

The membership has provided many speakers for both lay and medical organizations on a variety of topics, such as smoking, cancer of the lung, air pollution, tuberculosis, and other chest conditions. These have been provided to the various Christmas Seal organizations, local medical societies, schools, and others.

The Society is particularly interested in encouraging the teaching of pulmonary disease at both the graduate and undergraduate levels. It provides support for two or three residents to attend the annual tri-state Pembine Conference.

The range of topics presented has been truly broad and stimulating, reflecting the vast changes in knowledge and experience of cardiopulmonary diagnosis and treatment in the last half century.

Individuals of prominence in the field of pulmonary disease who have been or are members of the Society are: Drs. Corwin Hinshaw, Ejvind Fenger, Thomas Kinsella, Karl Pfuetze, P. M. Mattill, John F. Briggs, Sumner Cohen, Arthur M. Olsen, James F. Hammarsten, William B. Tucker, David Carr, Richard V. Ebert, Howard Andersen (currently chairman of the state Pollution Control Agency). There are many others. Dr. A. Falk of the Veterans Administration Hospital serves as Secretary-Treasurer and deserves great credit for maintaining the continuity of the Society.

The problems and the solutions change inexorably with the passage of the years; the need for the value of a society committed to the stimulation of scientific study continues.

D. S. Fleming, M.D.
Past President*
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*Dr. Fleming's term of office expired November 1, 1971. Dr. Howard A. Andersen is the new president of the Society.

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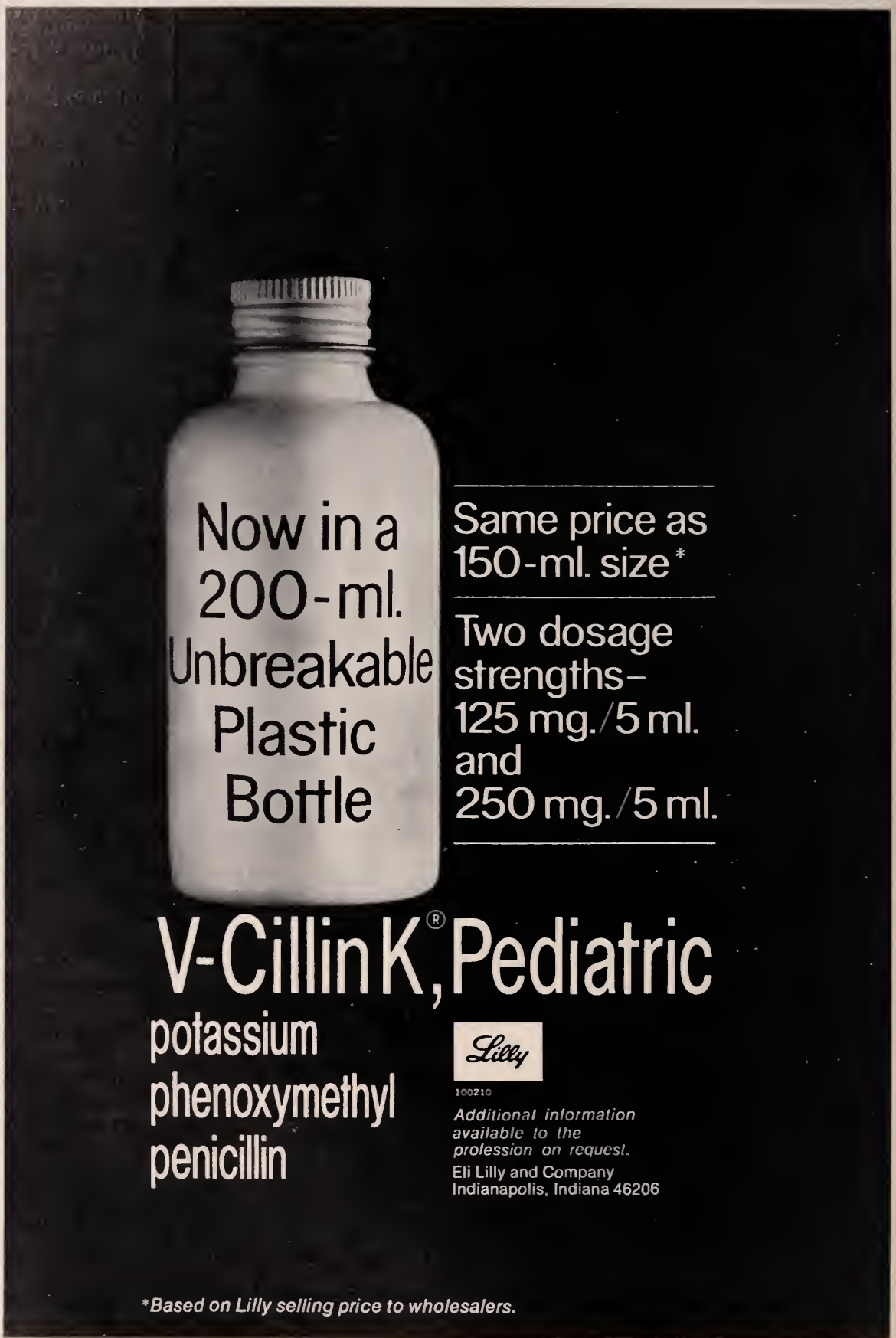
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Recurrent Major Ventricular Arrhythmias

Associated with Thioridazine Therapy

RUDOLPH J. ROSENQUIST, M.D.,* WILLIAM W. BRAUER, M.D.,* AND JOHN N. MORK, M.D.*†

UNEXPLAINED SUDDEN DEATH in psychiatric patients is a cause of considerable concern. Recent reports show an association between phenothiazine therapy and sudden death.[1,2] Unexplained sudden deaths in psychiatric patients are presumed to result from major ventricular arrhythmias, although these arrhythmias have been documented only in patients taking thioridazine (Mellaril). This case study describes the development of major ventricular arrhythmias in a patient taking thioridazine.

Case Report

History

A 32-year-old housewife has a 10-year history of manic-depressive psychosis of the circular type. A hospitalization in November, 1959, for manic behavior required 17 electroshock treatments to bring about a remission. In December, 1967, she was rehospitalized due to hypomania. She was treated with thioridazine and temporarily continued with a dose of 50 mg. four times a day as an outpatient. In January, 1968, she was again hospitalized for depression and treated with antidepressants. Another manic attack in March, 1968, necessitated a fourth hospital admission; she was treated with drugs, including lithium carbonate, 600 mg. three times a day and thioridazine, 50 mg. four times a day.

In December, 1968, a further manic episode was treated with hospitalization and drugs. These included lithium carbonate, 600 mg. three times a day and chlorpromazine (thorazine), 100 mg. every four hours. Her failure to improve, despite the serum lithium level of 2 meq/liter (therapeutic range 0.5 to 2.0 meq/liter), prompted the use of electroshock treatment on January 19, 1969. Following two consecutive electroshock treatments, she has a 45-minute episode of apnea which was managed successfully with assisted ventilation. During this apneic period, she did not have any cardiac arrhythmia. The serum potassium level during the episode was 3.9 meq/liter. She improved and was released from the hospital on January 31, taking lithium carbonate, 300 mg. three times a day and chlorpromazine, 50 mg. four times a day. Later, on February 21, 1969, thioridazine, 50 mg. four times a day was substituted for the chlorpromazine.

She was seen on February 25, 1969, as an outpatient because of increasing mania. Her serum lithium level at this time was 1.1 meq/liter. Two days later, she was returning to the hospital for an outpatient visit when her husband observed that she had slumped to the car floor. She roused and then lost consciousness a second time. When she arrived in the emergency room at 1:00 p.m., her blood pressure and pulse were unobtainable and an electrocardiogram was obtained (Figure 1a). An intravenous bolus of 50 mg. of lidocaine, together with external cardiac massage, produced conversion of the abnormal rhythm to a sinus rhythm with premature ventricular contractions (Figure 1b).

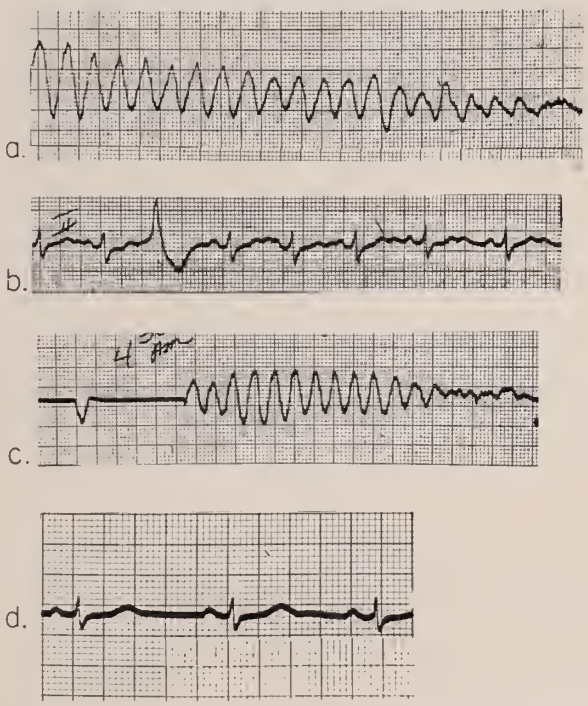


Fig. 1—Electrocardiograms of standard limb lead II (a) taken at the time of admission on 2-27-69 showing ventricular tachycardia with a rate of 250 per minute, (b) taken immediately after the initial resuscitation showing a prolonged QT interval, sinus arrhythmia, a premature ventricular complex and a prominent U wave, (c) taken at 4:30 a.m., 2-28-69, showing ventricular tachycardia with a rate of 300 per minute transforming into ventricular fibrillation at the end of the strip and (d) taken on 3-10-69 showing a return to normal.

*University of Minnesota Medical Unit, Northwestern Hospital, Minneapolis, Minnesota.
†Current address: Worthington Medical Center, Worthington, Minnesota.

Later questioning revealed that the patient had taken "too many" of her lithium capsules and thioridazine tablets approximately five days before admission. Following this, she took "less than" the prescribed number of tablets and noted excessive thirst and frequent urination. A single fainting episode occurred the evening preceding the day of admission. She denied taking any digitalis or any other cardiac drug.

The patient had no specific history of anginal pain, hypertension, or diabetes. The family history was remarkable for its lack of cardiovascular disease. She had been in good physical condition on all previous admissions. She had no diarrhea or fever.

Physical Examination

Physical examination on February 27, 1969, revealed a disheveled young woman with rambling speech. Blood pressure was 134/80 mm. Hg and pulse rate, 80/minute (during sinus rhythm). The chest was clear to auscultation and percussion. The heart sounds were of normal intensity and the second sound was physiologically split. A short, early grade 2/6 systolic murmur was heard best at the apex. The remainder of the physical examination was within normal limits.

Laboratory Data

On the day of admission, an electrocardiogram showed a prolonged QT interval, flattened T waves, and prominent U waves. The serum potassium was 3.3 meq/liter immediately following the initial hypotensive cardiac arrhythmia. Other serum electrolytes were sodium, 134 meq/liter CO_2 content, 21 meq/liter, chlorides, 105 meq/liter, lithium, 1.4 meq/liter, and magnesium, 1.6 meq/liter. The phenothiazine serum level was 3.3 mg/100 cc. On the following morning, the pH was 7.42 and serum calcium, 10.0 mg/100 cc. Creatinine clearance on March 3 was 111 cc/minute, and on March 14, 130 cc/minute. Phenolsulfonphthalein excretion was 60% at one hour on March 5. Urine sediment was within normal limits. Urine specific gravity was 1.007 on February 27, 1969, and by March 6 was consistently above 1.010. Chest x-ray showed a normal cardiac silhouette.

Potassium intake was measured by oral and IV replacements. Urine potassium loss was measured and subtracted from the potassium intake to obtain the balance (Table 1 and Figure 2). During the period of positive potassium balance, the electrocardiogram improved but remained abnormal with T wave flattening and a prolonged QT interval on March 4, 1969. By March 10 the electrocardiogram had returned to normal (Figure 1d).

TABLE 1

Potassium Balance Data

Values in Meq. Potassium										
Oral plus intravenous intake potassium	180	341	308	274	387	120	332	234	174	
Urinary output potassium	72	275	261	220	220	165	185	186	126	
Balance potassium	+108	+66	+49	+54	+167	−45	+148	+48	−48	
	9 am	9 pm	9 am	9 pm	9 am	9 pm	9 am	9 pm	9 am	9 pm
Date	2/27		2/28		3/1		3/2		3/3	

Course

Following the initial episode of ventricular tachycardia and vascular collapse, the patient had recurrent episodes of ventricular tachycardia and/or ventricular fibrillation during the day of February 27. Several episodes responded to external cardiac massage, but approximately twenty episodes required electrical defibrillation (the standard dose delivered being 200 watt-seconds). Intravenous lidocaine and pronestyl were tried in high dose without success. Correction of a presumed potassium deficiency was the sole means of treatment of the cardiac arrhythmia after 5:30 p.m. on February 27 (Figure 2). During the evening of the same day, the arrhythmic episodes were less frequent, and the last episode of ventricular fibrillation (Figure 1c) was converted by electrical defibrillation at 4:30 a.m. the next day.

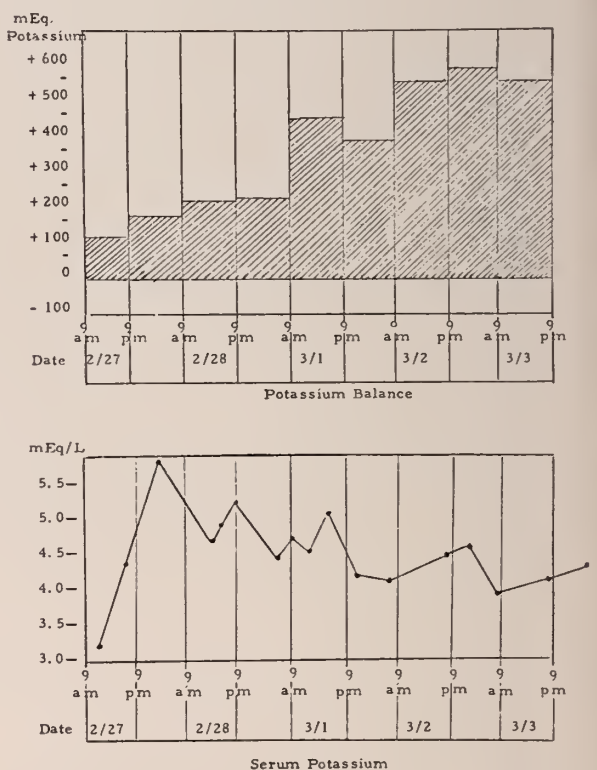


Fig. 2—A positive potassium balance is graphically demonstrated above (see Table 1 for actual data). The serum potassium levels are graphically demonstrated below.

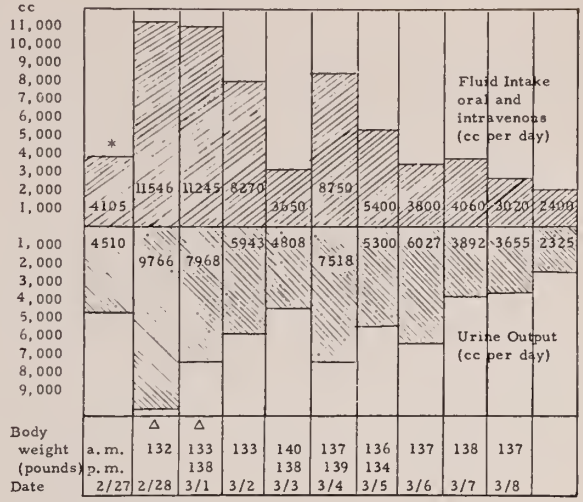
Following the arrhythmic episodes, the patient's major problems were the continued polyuria and the manic phase of her psychosis. From the time of admission, the urine output was excessive (Figure 3). Over the first two hours of hospitalization, the urine output measured 785 cc. while the total intake during this period was only 250 cc. intravenously. Subsequent hourly outputs were frequently in excess of 500 cc., and once, 760 cc. of urine

was excreted in a one-hour period. A decrease in hourly urine volume occurred transiently on February 28 after an injection of 0.5 cc. pitressin tannate in oil. Another transient decrease in hourly urine volume followed the injection of 1.0 cc. pitressin tannate in oil on March 1. Without further pitressin the urine output returned to a normal level after the first week (Figure 3).

The patient slept for only one hour during her first three days in the hospital. She talked almost constantly, had frequent delusions, and became progressively more disoriented. She was finally sedated by a combined drug regimen of thorazine, 600 mg. a day and pentobarbital, 600 mg. a day. Subsequently, she improved to an ambulatory status without clinical evidence of an organic brain syndrome. She was discharged from the hospital on April 2.

Discussion

Sudden death associated with phenothiazines has been attributed to cardiac arrhythmias.[1,2,14] It is noteworthy that ventricular tachycardia or fibrillation is documented for only one member of the phenothiazines, thioridazine. The descrip-



*Eleven hour specimen.
Δ - Pitressin administered.

Fig. 3—A graphic demonstration of fluid intake (above) is contrasted with urine output.

TABLE 2

Thioridazine-Induced Ventricular Arrhythmias

Case No.	Age	Sex	Thioridazine dose mg/day (duration)	Concurrent phenothiazines (mg/day)	Serum potassium (mEq/liter)	Type	Therapy: Not successful	Therapy: Successful	Fatal outcome
1 Kelly et al. (22)	46	F	600-3600 (2 months)		—	VT	supportive		+
2 Kelly et al. (22)	57	F	1000-1500 (7 months)		—	VT	supportive incl. D		+
3 Desautels et al. (20)	—	—	1500 (2½ months)		—	VT		methoxan-amine, P	
4 Hollister et al. (14)	40	M	1600 (6 days)	trifluoperazine (20)	—	VF	C, D, Dn, P		+
5 Schoonmaker et al. (23)	50	M	600 (6 days)		4.2	VT	Q, P, A, C	pacemaker	
6 Giles et al. (21)	19	M	900 (5 days)	perphenazine (32)	wnl	VT	L, P, C		
7 Tranum et al. (15)	47	M	75 (?) then 250 (2 weeks)		3.4* 3.2**	VT, VF	I, P, L, C	pacemaker	+
8 Rosenquist et al. (present case)	32	F	200 (6 days)		3.3	VT, VF	L, P, C	potassium	

Abbreviations:
C = countershock
D = digitalis preparation
Dn = sodium diphenylhydantoin
P = procainamide
Pl = proparolol
L = lidocaine
I = isuprel
E = epinephrine
Q = quinidine
VT = ventricular tachycardia
VF = ventricular fibrillation
wnl = within normal limits

*Potassium value for first and **second day of arrhythmia in this case.

tion of major ventricular arrhythmias associated with thioridazine therapy gives impetus to the idea that thioridazine was a causative factor in this patient's recurrent ventricular tachycardia and fibrillation.

Since 1963, eight cases have been reported in which ventricular arrhythmias were associated with thioridazine therapy (Table 2). Those cases without reported hypokalemia had quite high daily doses, ranging from 600 to 3600 mg. per day. The present case and the case of Tranum and Murphy[15] both had mild hypokalemia and recurrent major ventricular arrhythmias with a much lower daily dose of thioridazine (Table 2).

Thioridazine may produce these arrhythmias through an effect on adenosine triphosphatase (ATPase)[1]. Adenosine triphosphatase activity is an integral part of the mechanism of trans-membrane ionic flux.[1,16] Inhibition of adenosine triphosphatase activity in cardiac muscle is associated with increased myocardial irritability.[16] As Leetsma and Koenig[1] suggest, phenothiazines may have an inhibitory effect on adenosine triphosphatase comparable to that of digitalis. Since the potassium ion is reported as a secondary activator of adenosine triphosphatase,[16] hypokalemia can be expected to cause further inhibition of adenosine triphosphatase. Therefore, decreased adenosine triphosphatase is a potential common pathway for the production of major ventricular arrhythmias with phenothiazine therapy and hypokalemia. Thioridazine-induced changes in the electrocardiogram do mimic those of hypokalemia[17,18] and, although the serum potassium remains normal,[19] these electrocardiographic changes can be corrected by administration of potassium salts.[19]

Several reports of major ventricular arrhythmias attributed to hypokalemia do not completely exclude a second causative factor.[3-8] Experimentally, hypokalemia spontaneously induces ventricular fibrillation[9,10,11] or facilitates its production by electrical stimulation[12,13] in isolated animal heart preparations. These phenomena are reversible with potassium repletion.[11,12,13] Thus, in animal preparations, hypokalemia alone can induce major ventricular arrhythmias. From the paucity of well documented cases, it appears that in humans another adverse factor is usually necessary.

With the mild reduction in serum potassium (3.3 meq/liter) we cannot implicate hypokalemia as a major cause of this patient's ventricular arrhythmias (Figure 2). Electrocardiogram evidence (Figure 1-b) and the response to potassium replacement would all indicate a possible role for a potassium deficiency in the genesis of the ventricular arrhythmias. Certainly the intentional combination of hypokalemia and thioridazine therapy would appear dangerous on theoretical grounds.

There is no satisfactory explanation for the diabetes-inspidus-like state. It might represent a hitherto undescribed side effect of one of the drugs which the patient was taking or simply excess water ingestion secondary to the patient's manic state. We know of no evidence which would link lithium to the production of ventricular arrhythmias.

Summary

A case of recurrent ventricular tachycardia and fibrillation in a 32-year-old manic-depressive woman is reported. The patient received thioridazine, chlorpromazine and lithium. Of the phenothiazine drugs, only thioridazine therapy has been documented as a cause of major ventricular arrhythmias. Thioridazine therapy and possibly hypokalemia are considered to be likely causes of this patient's arrhythmias. Treatment of this patient with electrical defibrillation, potassium replacement, and drug withdrawal was successful. It is proposed that intentional hypokalemia in patients receiving thioridazine poses a theoretically dangerous clinical situation.

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References may be secured from the author or the reprints.

Men occasionally stumble over the truth, but most of them pick themselves up and hurry off, as if nothing had happened.—Winston Churchill.

Pulmonary Geotrichosis and Candidiasis

RONALD OLIN, M.D.*

PULMONARY GEOTRICHOSIS is a rare disease caused by the fungus *Geotrichum candidum*. This fungus, like the yeast-like fungus, *Candida albicans*, is saprophytic in the earth and in decaying organic matter. Both organisms are also commensals in man where they can be found in the pharynx, mouth, skin, colon, and bronchopulmonary tree.[1] They have been reported to cause a variety of pathologic conditions, including conjunctivitis, tonsillitis, stomatitis, vaginitis, cutaneous lesions, ulcerative proctitis, and bronchopulmonary disease.[2] They can also result in a life-threatening fungemia with endocarditis, meningo-encephalitis and metastatic abscesses anywhere in the body.[3,4]

Human bronchopulmonary mycoses may be secondary to other lung diseases such as bronchiectasis and tuberculosis. Debilitating conditions such as diabetes, leukemia, and lymphomas may also be predisposing factors. Drugs such as steroids and broad-spectrum antibiotics have also been implicated as predisposing factors.

The ability of *Geotrichum* and *Candida* organisms to emerge as clinically significant pathogens is now recognized and, in addition to being opportunist invaders,[5,6] they are occasionally primary pathogens.[7,8]

This report describes a patient who developed an extensive left-sided pneumonitis followed one year later by a similar right-sided pneumonitis in which *Geotrichum candidum* and *Candida albicans*, respectively, were the etiologic suspects.

Case Report

A 64-year-old white male was referred for the evaluation of a persistent left lower lung infiltrate which apparently began about June 20, 1965, with a slight fever, malaise, weakness and productive cough (Figure 1A). This change was not present on chest x-rays from 1960 to 1964. The hemoglobin was 12.6 gm. percent and the leukocyte count 11,600 per cmm. A tuberculin skin test was 3+. Routine urinalysis, cold-agglutinin titer, complement-fixation test for psittacosis and a histoplasmin skin test were normal or negative. He was treated with dimethyl chlortetracycline (Declomycin) 300 mg. twice daily given orally until July 16, at which time another x-ray showed no change. Since the onset of the illness, he had been raising about one ounce of mucopurulent sputum per day. He denied chest pain, hemoptysis, anorexia, weight loss, skin rashes, bowel or urinary changes. He was taking digitoxin 0.2 mg. and Orinase 500 mg. daily and was using a Medihaler-Duo.

Past History

Pulmonary emphysema was first diagnosed in 1957, but he continued to smoke two packs of cigarettes a day until 1962. Effort dyspnea and easy fatigability necessitated his retirement in 1964. His pulmonary disability had not changed from his retirement to the present illness. Diabetes mellitus had been discovered in June 1964, and Orinase prescribed, but he took it irregularly. A duodenal ulcer had been known for approximately 25 years, but had been relatively inactive over the previous three years.

He had no pet birds and had not been out of Minnesota during the preceding six months. He had insulated his home in January 1965, and had fiberglassed the bottom of his boat in early May 1965. He had not used nosedrops or mineral oil.



Fig. 1A—July 9, 1965

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Physical Examination

The patient was an elderly white male who coughed frequently. His height was 69 inches and his weight 171 pounds. Blood pressure was 132 systolic and 66 diastolic, pulse 96 per minute, temperature 98.4 F, and respirations 24 per minute. There were no palpable lymph nodes. Chest expansion was poor and coarse crepitations were heard over the left lower chest anteriorly and posteriorly. There was early finger clubbing and slight cyanosis of the lips and fingernails.

Laboratory Studies

When he was hospitalized on August 2, he was found to have a concentration of hemoglobin of 11.8 gm. percent, hematocrit of 39 percent, leukocyte count of 10,600 per cmm. with a differential of 7 percent lymphocytes, 82 percent segmented neutrophils, 9 percent band neutrophils, 1 percent eosinophils and 1 percent metamyelocytes. The erythrocyte sedimentation rate was 96 mm. per hour (Westergren). Routine urinalysis was normal. Cold agglutinin titer was negative. The fasting blood sugar was 109 mg. percent (normal 70-90 mg. percent). Serum protein electrophoresis, serum calcium and phosphorus, blood urea nitrogen, bromsulphthalein dye test and serum electrolytes were normal. Coccidioidin, blastomycin, histoplasmin and purified protein-derivative intermediate skin tests were negative.

X-ray Findings

A chest x-ray (Figure 1B) revealed a marked change in the left lung *since* July 9 and 16, as there was no longer a diffuse mottled infiltration involving the upper and lower lobes; rather the left lung was almost diffusely opaque. There was some shift of the heart and mediastinum to the left side and some elevation of the left hemidiaphragm. The right lung was clear and appeared moderately emphysematous. The heart size appeared to be within normal limits.



Fig. 1B—August 5, 1965

A 12-lead electrocardiogram revealed slight, rounded sagging of the S-T segments in leads II, III, AVF, V_4 to V_6. The maximum breathing capacity was 33.6 liters per minute with a predicted normal of 105 liters per minute (68 percent below normal). The vital capacity was 2.4 liters with a timed one-second of 1.1 liter.

Bronchoscopy

On August 3, this procedure revealed chronic inflammatory changes of the mucosa of the left main bronchus and tributaries. No endobronchial lesions or exudative changes were seen. Bronchial washings obtained from the left side resulted in a slight growth of *Staphylococcus albus.*

Although afebrile in hospital, he demonstrated dyspnea at rest and continued to cough up one to two ounces of mucopurulent sputum daily.

Treatment

Procaine penicillin G, one million units intramuscularly, every 12 hours, tetracycline hydrochloride (Achromycin-V) 250 mg. orally every six hours, and Alevaire 0.5 cc. with crystalline penicillin 50,000 units by inhalation four times daily, were given empirically from August 4 to 17.

Diagnosis

A chest x-ray on August 16, 1965 revealed essentially no change in the appearance of the left lung. Sputa for fungal cultures collected on August 10, 11, and 12 each revealed pure cultures of *Geotrichum candidum.*

August 17

On this date, treatment was changed to potassium phenoxemethyl penicillin (V-Cillin-K) 250 mg. and prednisone 10 mg., both given orally every six hours. The patient then began to have less dyspnea and cough.

August 23

On this date, chest x-ray revealed slight clearing of the process in the left upper and lower lobes.

August 31

Breath sounds were diminished over the left lung. A chest x-ray showed there was a pneumothorax on the left side with a layer of air one inch in thickness over the left upper lung and about one-half inch in thickness at the left base. The left lung appeared to be more aerated, especially in the upper portion, and the density of the pulmonary infiltration was less homogeneous.

September 10

When seen on this date, the patient felt fairly well. A chest x-ray revealed the pneumothorax to have largely cleared with only a small amount of air overlying the upper lobe.

September 24

He was seen for the last time at the Fargo Clinic on this date when he had only minimal dyspnea and cough and weighed 174 pounds.

November 30

The patient then returned to the care of Dr. Robert N. Watson of the Lake Region Clinic, Detroit Lakes, Minnesota, who saw him on the given date. The patient had felt well enough to hunt deer in the fall. Some morning cough persisted, but he was taking no medication. Examination revealed rales at the right base. A chest x-ray (Figure 1C) showed an area of infiltration with atelectasis and pleural reaction involving the posterior segment of the right lower lobe in the region of the costophrenic angle, the left lung was clear.



Fig. 1C—November 30, 1965.

July 1, 1966

On this date, he complained of moderately severe dyspnea, productive cough, hemoptysis and weakness of one week's duration. He was then hospitalized from July 5 to July 19, when examination revealed rales throughout the right lung. Blood pressure was 100 systolic and 84 diastolic, and cardiac examination revealed a rate 110 per minute with a gallop sound. The sedimentation rate was 70 mm. per hour; the fasting blood sugar, 140 mg. percent. A chest x-ray (Figure 1D) on July 5 revealed slight cardiac enlargement. There was a diffuse pulmonary infiltrate throughout the right lung, mostly in the right middle and lower lobes; the left lung was clear, the heart slightly enlarged. He was treated with oxygen, prednisone, isonizide, potassium iodide, and cloxacillin.

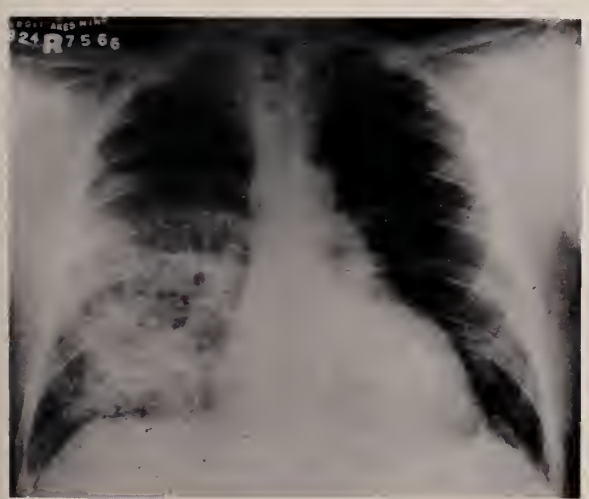


Fig. 1D—July 5, 1966.

July 18

On this date, a chest x-ray showed more loss of volume of the right lung, and the mediastinum was shifted. The lower right lung showed better aeration and the right diaphragm was tented. The left lung was clear. Sputa for acid-fast bacilli obtained on July 8, 11, 15, and 16 were negative via stain, culture and guinea-pig inoculation. Sputa for cytology were negative. Cultures of sputa for fungi obtained July 9 and 14 revealed a pure culture of "a yeast-like organism with hyphae which was morphologically and biochemically indistinguishable from *Candida albicans*" (Department of Health, Medical Laboratories, University Campus, Minneapolis).

August 9

On this date, the patient had less dyspnea and cough. A chest x-ray (Figure 1E) showed improvement, with clearing of the right middle and lower lobes.



Fig. 1E—August 9, 1966.

September 13

On this date, the patient complained of more dyspnea with some orthopnea. There was some edema of the ankles. The leukocyte count was 5,650 per cmm. A chest x-ray (Figure 1F) showed some further clearing of the right lower and middle lobe infiltrate. He was given diuretics.

October 31

On this date, the patient's right lung was clear to auscul-

tation.

November 10

On this date, he complained of a slight cough and dyspnea with moderate effort. The lungs were clear and the heart sounds regular.

He expired two weeks later and a coronary thrombosis was the presumed cause of death, although an autopsy was not performed.



Fig. 1F—September 13, 1966.

Geotrichosis Pulmonum

Geotrichum candidum was described by Link in 1809 to include fungi with septate mycelia which fragment into large square-ended arthrospores. The identity of the fungus was further clarified by Carmichael in 1957[9] who described the natural habitat and cultural characteristics of 52 strains of *G. candidum* and also noted 55 synonyms found in the older literature.

Geotrichosis has been commonly described in Brazil where it is thought to be responsible for 1 to 1½ percent of lung infections.[10] The disease has also been reported in Great Britain, France, Scandinavia and North America. Smith in 1934[11] reported five nonfatal cases of bronchopulmonary geotrichosis and emphasized that patients with chronic bronchitis or other pulmonary disease who have white mucoid sputum with grayish flecks should be suspected of having geotrichosis. By 1935 Dodge[12] had noted 12 cases of *Geotrichum* infection, eight of which were respiratory infections. Reeves in 1941[13] reported 79 cases of bronchopulmonary mycoses in the Southern United States, including two cases of geotrichosis pulmonum. In 1947 Smith[14] surveyed 250,000 hospital admissions and found four cases of geotrichosis among a total of 207 cases of fungal disease. Kunstadter and coworkers in 1950[15] described five members of one family (three children and their parents) with positive skin tests to *Geotrichum* extract. In 1952, Kaliski[4] reported a case of miliary tuberculosis in a two-month-old Mexican infant which was complicated by *Geotrichum septicemia.*

In 1952 Bendove and Ashe[16] described a case of *Geotrichum* fungemia in a 79-year-old diabetic. Webster in 1959[17] described three cases of pulmonary geotrichosis complicating pulmonary tuberculosis, Friedlander's pneumonia and pulmonary emphysema, respectively. In 1962 Bell and coworkers[18] described a 57-year-old man with bronchopulmonary geotrichosis whose asthmatic attacks responded to symptomatic therapy, but whose sputum remained positive for *Geotrichum.*

Nasser and Daly in 1965[8] reported a case of bronchopulmonary geotrichosis which did not respond radiologically to iodides. In 1966 Ross and coworkers[19] described a previously healthy 46-year-old woman who developed bronchitis and asthma and whose sputum cultures revealed *Geotrichum candidum.* The patient had been planting bulbs, and the organism was cultured from the bulb-potting fibre.

Candidiasis Pulmonum

Castellani[20] in 1906 was consulted by a tea-taster because of chronic cough, who described his disease as "tea-taster's cough" and related that he had developed the cough after inhaling and tasting crushed tea leaves. Numerous mycelial fragments and yeast-like bodies were isolated from his sputum and identified as *Monilia.* These organisms were insufflated into the respiratory tract of guinea pigs and the animals died from pneumonia.

Boggs and Pincoffs in 1915[21] described the first case of pulmonary moniliasis in the United States. Although pulmonary moniliasis is found in all climates and among all racial, age and sex groups, its exact incidence is unknown. In addition, the classification of *Candida* organisms isolated from man has presented many difficulties. Mycologists are not in agreement as to the number of species which should be included in this group of yeast-like organisms, but the system suggested by Martin and coworkers[22] is widely

used. *Candida albicans* is the member of the genus commonly associated with disease processes in man.

In 1924 Steinfeld[23] reported a series of patients with bronchial asthma in whose sputa *Monilia* was present. Galbreath and Weiss in 1929[24] reported a patient whose clinical features suggested pulmonary tuberculosis but in whose sputum *Monilia pinyoni* (ashjordi) organisms were seen consistently and acid-fast organisms were absent. In 1929 Craik[25] reported a patient with bronchitis and asthma, and *Monilia* was isolated from the sputum. Reeves in 1941[13] noted that *Monilia* was the agent in 40 of 79 cases of bronchomycoses of one month to five years' duration seen in the southern United States. In 1946 Tarnell[26] described several cases of "thresher's lung" in which *Monilia* was the etiologic suspect.

Greer and coworkers in 1948[27] reported the isolation of *Monilia* from the sputa of 45 of 310 consecutive patients admitted to the Houston Tuberculosis Hospital, in 18 of whom the fungus was found in specimens obtained by intratracheal aspiration. In 1951 Oblath and coworkers[7] reported six cases of pulmonary candidiasis with postmortem findings in one case; they emphasized that *Candida albicans* was truly pathogenic in man.

The role of *C. albicans* in bronchial asthma was noted by Keeny in 1954.[29] A survey by Chakravarty and Sandhu in 1962[30] found that bronchopulmonary candidiasis complicated 3.7% of chronic bronchopulmonary diseases. In 1967 Chakravarty[31] reported 11 patients with bronchopulmonary candidiasis. He suggested that patients with chronic bronchitis who do not improve with conventional treatment be investigated for bronchopulmonary candidiasis.

Clinical Manifestations

There are no pathognomonic symptoms or signs of bronchopulmonary geotrichosis or candidiasis. They can simulate chronic bronchitis, bronchiectasis, other mycoses, malignancy, pulmonary tuberculosis or lung abscess. The pulmonary type is rare but more serious than the so-called bronchial type. The sputum of patients having pulmonary geotrichosis may be earthly-smelling and of a peculiar mucoid or gelatinous type with "grayish flecks.[11]" Rusty sputum, purulent sputum[18] and frank hemoptysis have also been reported.[28]

Diagnosis

Chest x-rays are not diagnostic for bronchopulmonary geotrichosis or candidiasis without cultural proof. The chest x-ray can be normal; it can reveal diffuse peribronchial thickening; or it may show dense patches of infiltrate or thin-walled cavities. The roentgenologic findings can be confused with neoplasm, other mycotic infections, sarcoidosis, tuberculosis and chronic bacterial pneumonias.[17]

It is emphasized that these organisms should not be regarded as pathogenic unless found in large numbers in repeated fresh specimens of sputa.[4] The mere presence of G. *candidum* or *C. albicans* in the sputum is not indicative of disease since they are frequently seen in normal sputa and may be found in association with almost any pulmonary disease. Ross and coworkers[19] isolated *Geotrichum candidum* from the sputum on 73 occasions. They also grew it from the trachea and bronchi at bronchoscopy, as did Minton et al.[28] Chakravarty[30] recommended that the sputum should be positive consecutively at least four times for *C. albicans* and it should show heavy growth on culture.

Lung or bronchial biopsy with detection of *G. candidum* or C. *albicans* in the tissue is the surest method of diagnosis; but this is not practical in daily practice. Chakravarty[30] performed a bronchial biopsy in four patients, and the yeast cells were identified in the bronchial tissue.

Skin tests, agglutination tests, complement-fixation tests and precipitation tests for these organisms have been described but are not dependable for accurate diagnosis. Skin tests may be negative in the presence of a severe infection. In support of their diagnosis, Ross and coworkers[19] noted a thirty-fold rise in their patient's serum of *Geotrichum*-agglutinating antibodies.

Mycologic Diagnosis

Geotrichum candidum reproduces in culture by segmentation of the hyphae into arthro-spores. It grows readily at room temperature and at 37° C. on Sabouraud's media and develops a dry,

mealy surface. Microscopically it is identified by the rectangular conidia. *Candida albicans* can also be grown on Sabouraud's media at 37° C. and appears as creamy, moist to dull colonies with a distinct yeasty odor. In fresh preparations or gram-stained smears, the organisms appear as small, oval, thin-walled, budding yeast-like cells with or without accompanying mycelial elements.

Treatment

Many forms of therapy have been used for bronchopulmonary geotrichosis. Radiotherapy was attempted by Kunstadter and coworkers[15] with questionable success. Iodides have been used in the form of intravenous sodium iodide or oral supersaturated solution of potassium iodide, also with limited success.[8,15] Bendove and Ashe[16] used neomycin intravenously to treat a patient with *Geotrichum* septicemia; but clinical improvement was overshadowed by the development of total deafness. Bell and coworkers[18] used potassium iodide orally and then oral Nystatin and Nystatin inhalations for 12 weeks without eradication of the fungus. Ross and coworkers[19] attempted to desensitize their patient with a course of solutions of increasing concentration of *Geotrichum candidum* extract, but benefit was limited. The fungus was sensitive to colistin given intramuscularly and by inhalation, but complete eradication of the fungus was not obtained.

Treatment of pulmonary candidiasis has also been difficult. Before 1950, medications mentioned most prominently were the iodides given either orally or intravenously, and ethyl iodide given by inhalation, and iodized poppyseed oil administered intratracheally.[7] Chakravarty[31] reported that five of 11 patients with bronchopulmonary candidiasis who received oral Nystatin tablets and Nystatin aerosol improved clinically, and the sputum became negative for *C. albicans*. Amphotericin-B is required in severe infections and in disseminated candidiasis with reported variable success.[3] There are no reports of its use in pulmonary or disseminated geotrichosis.

Prognosis

It should be noted that the prognosis for bronchopulmonary geotrichosis or candidiasis in the absence of concomitant disease or complications is usually excellent and the disease may terminate without therapy.

Discussion

The patient had two debilitating conditions, namely, chronic obstructive pulmonary emphysema and adult-onset diabetes mellitus, which were likely predisposing factors to his mycotic infections. The exact nature of the initial left lower lobe pneumonia in early July 1965 is uncertain. In one month's time the infiltrate occupied the entire left lung. Although lung biopsy was considered, the patient was too ill at the time. Steroids and antibiotics were used empirically and improvement occurred despite a complicating pneumothorax. *Geotrichum candidum* was isolated in pure culture on three consecutive specimens of sputa, but the reports were not received until six weeks later when the patient was improving. It is known that *Geotrichum* is sometimes found in normal trachobronchial flora. However, the diagnosis of pulmonary geotrichosis seemed warranted by the negative tuberculin, histoplasmin, coccidiodin and blastomycin skin tests and the absence in the sputum of malignant cells, other fungi and acid-fast bacilli.

The patient did fairly well clinically for several months and then developed an infiltrative process of the right lung in July and August of 1966. There were no predisposing medications to implicate at this time. Treatment including iodides was again used and improvement gradually occurred. Because no other organisms were isolated from the sputum, it was felt that *Candida albicans* was the etiologic agent.

Summary

A 64-year-old man with chronic obstructive pulmonary emphysema and adult-onset diabetes mellitus developed an extensive left-sided pneumonitis in which *Geotrichum candidum* was the etiologic suspect. This resolved with nonspecific therapy. One year later he developed a similar, extensive, right-sided pneumonitis with *Candida albicans* as the etiologic suspect. This was improving at the time of his death from cardiac disease.

Acknowledgement

The author wishes to thank Dr. R. N. Watson of the Lake Region Clinic, Detroit Lakes, Minnesota, for making available the patient's records and chest x-rays.

References may be secured from the author or the reprints.

To err may be human, but to admit it isn't.—Herbert Prochnow

Laparoscopic Sterilization*

P. P. WILLIAMS, M.D.* AND R. P. BENDEL, M.D.†

As INTEREST in laparoscopy has grown in recent years, it has become increasingly evident that the technique lends itself well to limited operative procedures, thereby circumventing full-scale laparotomy. Included in this group of procedures is tubal fulguration and partial salpingectomy, i.e., sterilization.

Unlike the basic 70-year-old technique of laparoscopy, sterilization via the laparoscope dates back only some 30 years.[1,2] Nearly 25 more years elapsed before the next reports appeared in the literature in the mid-1960s.[3] Since then, additional experience has been reported with increasing frequency.

Technique

Instruments

The basic instruments for laparoscopic sterilization are those for diagnostic laparoscopy: the laparoscope with fiber-optic cable and distal light source, a pneumoperitoneum needle and pressure-flow regulated carbon-dioxide supply, the valved and straight trochar-cannulas, and the ancillary vaginal instruments. In addition, we use a biopsy forceps or the Cohen-Eder instrument for the actual tubal interruption. The latter is a conductive, insulated tong-type forceps with a cylindrical cutting sleeve which can be advanced over the tongs to remove pieces of the tube.

The Scope

When the scope has been introduced and the pelvic organs are under direct visualization, the abdominal wall is transilluminated in either lower quadrant so that blood vessels may be avoided, and the small trochar-cannula is introduced. This cannula will accept the biopsy tongs.

The Cautery

The biopsy tongs are passed through the cannula and, under direct vision, a fallopian tube is grasped approximately two centimeters from the uterine cornu. With the tube on slight tension and the tip of the forceps free of other tissue, a wave of cautery current is turned on. It is usually necessary to maintain this for four to six seconds, until the radial blanching which appears extends approximately one centimeter beyond the tip of the instrument. When the segment of tube has been coagulated, the cylindrical cutting sheath is advanced down over the tip, the current applied briefly, and the specimen removed without retracting the sheath. This same procedure is then repeated on the opposite side. Additional pieces of tube may be removed proximally or distally if a larger defect is desired. The separated stumps may be easily visualized, re-grasped, and cauterized, should hemostasis be incomplete. The instruments are removed and the pneumoperitoneum is evacuated. Postoperative discomfort is minimal and the patient is usually discharged from the hospital the next day. Normal activities are resumed within the week.

Figures 1-3 show high points of the procedure.

Experience:

Laparoscopy was begun at University of Minnesota Hospitals approximately 15 months ago. The majority of our 100 cases have been done

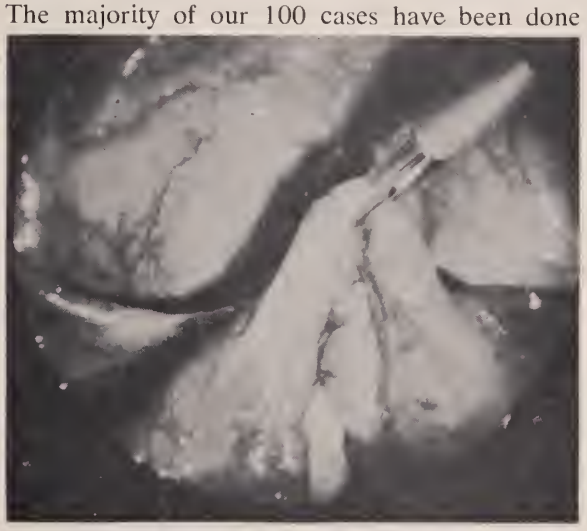


Fig. 1—The tube is grasped 1 - 2 cm. from the uterine cornu and placed on tension.

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*See Diagnostic Laparoscopic, September issue, Minnesota Med 54:781, 1971.

for diagnostic purposes.[4] As our experience with the basic technique grew, we became enthusiastic about sterilization via laparoscopy and this has now become our method of choice for interval sterilization. Reports from other centers have fueled our enthusiasm.

The average failure rate in six series[3,5,6,10,11,12] of laparoscopic sterilizations involving 2570 cases is 0.3%. Garb[13] reviewed many reported series of sterilization procedures done by more conventional methods and, in this review of 29,496 tubal sterilizations, he reported an overall failure rate of 0.71%. The favorable comparison, even with disparate totals, is evident.

Comment:

For most gynecologists laparoscopy represents a new and unproven procedure. Operative laparoscopy, generally, and tubal sterilization, specifically, are understandably even more foreign. We anticipate that familiarity will lead to acceptance.

Concerning the instruments for tubal interruption, we find very satisfactory results can be obtained with other than the Cohen-Eder biopsy tongs. The Palmer forceps, similar in design to the Cohen-Eder instrument, works equally well. We have also found a simple biopsy forceps satisfactory and have recently been impressed with a toothed biopsy forceps manufactured by ACMI. Regardless of the specific instrument employed, a provision for cautery must exist as the tube must be coagulated before it is divided. Care must be taken to insure that the tip of the instrument is free of other structures, particularly bowel, before the current is applied. If the Palmer or Cohen-Eder instruments are used, a potential hazard exists in advancing the cutting sleeve too far.

With the coagulation process, alteration in the histology of the excised portion of the tube is unavoidable, but adequate tissue confirmation is still possible.

The low failure rate associated with laparoscopic sterilization, compared with the failure rate of the conventional methods, makes laparoscopic sterilization even more appealing when considered from the standpoint of cost, duration of hospitalization, and minimum disability in the post-operative period. Our own experience is that patients having undergone laparoscopy are, with rare exceptions, ready to be discharged the morning after the procedure and resume all normal activities almost immediately. This set of circumstances is certainly preferable to the minimum four to five-day hospitalization and attendant restriction of activities when other means of sterilization are employed. While vasectomy has become increasingly popular as a means of permanent contraception, it will never completely answer the need. In many families it will remain the woman's responsibility to provide contraception. Laparoscopic tubal sterilization definitely appears to be a competitive procedure from the aspects of cost, effectiveness, and convenience.



Fig. 2—Application of the current produces the desired 1 cm. of radial blanching.



Fig. 3—The tube is interrupted and the stumps can be easily visualized.

References may be secured from the author or the reprints.

There are more old drunkards than old doctors.—Benjamin Franklin.

Dandy-Walker Malformation

Association with Syringomyelia

GEORGE S. BAKER, M.D.* AND RALPH E. RYDELL, M.D.†

In the adult patient, the diagnosis of massive posterior fossa cyst is often difficult prior to surgical exploration because the obstructing lesion may be either cerebellar tonsils herniating through the foramen magnum, as in the Arnold-Chiari malformation, or an arachnoid cyst associated with syringomyelia. However, when there is a large accumulation of cerebrospinal fluid in the posterior fossa, the patient being operated on for the Dandy-Walker malformation should be in the face-down cerebellar position to avoid sudden loss of a large quantity of fluid and its replacement with air. The Arnold-Chiari malformation is best explored with the patient in the upright cerebellar position, as this operation seldom is complicated by loss of large amounts of cerebrospinal fluid. When syringomyelia is present and a dilated central canal is noted at the obex, we have used a piece of occipital muscle to plug the opening with good success once the obstruction of the fluid is released and normal channels of circulation are established.

Presenting Complaints

The majority of patients who reach adult life with some form of embryonal malformation are considered to have arrested hydrocephalus, and the indications for neurosurgical procedures have included convulsive seizures, headaches, dissociated sensory disturbances, foot drop, and signs of intracranial pressure. Some of the important pathologic and roentgenographic features of the Dandy-Walker malformation in adults will be reviewed, and two interesting cases will be described.

Review of Literature

The term "Dandy-Walker syndrome" was coined by Benda[1] to refer to hydrocephalus with a large, cyst-like fourth ventricle. Dandy and Blackfan,[2] in 1914, gave the first detailed description of such a case and defined the pathologic aspects. Earlier reports of such cases probably had been published, but descriptions were too vague for identification. Taggart and Walker,[3] in 1942, described three cases, delineated the roentgenographic features, and pointed out that before the Dandy and Blackfan paper, other authors had not recognized this disease. Thus they established it as a clinical entity.

Obstruction of Foramina

Dandy and Blackfan correctly noted the absence of the foramina of Magendie and Lushka. On reviewing the embryology of the cerebellum and fourth ventricle, Taggart and Walker thought that the basic malformation was the failure of the foramina to thin and perforate in the fourth month of development. This proposal has been disputed by Brodal and Hauglie-Hanssen,[4] Benda,[1] and Gibson,[5] each having his own hypothesis. The four other mechanisms proposed were reviewed by D'Agostino and associates,[6] who tended to agree with Gibson that a posterior fourth ventricle malformation is responsible. It appears that the term "syndrome" is a misnomer since the clinical signs and symptoms are very inconstant. However, there is general agreement that an embryonic malformation is responsible; thus "Dandy-Walker malformation" is a better term.

Clinically Rare

Although the Dandy-Walker malformation is rarely encountered clinically, Benda found six cases in 13 consecutive hydrocephalic autopsies and considered it the "most common type." At the Mayo Clinic, only nine autopsy cases were reported by D'Agostino, Kernohan, and Brown[6] in a 44-year period. Russell[7] had only one case.

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Read at the meeting of the American Academy of Neurological Surgeons, Colorado Springs, Colorado, October 6 to 9, 1968.

Normal Life Possible

An interesting feature is that many of these people reach adulthood, have normal intelligence, and live normal lives. Taggart and Walker had one patient who came to operation at age 59 years, and cases have been reported in patients more than 60 years of age. Operation for the relief of this obstruction has long been associated with a very high mortality.[8-10]

Cyst Extension Into Central Canal

Gardner and co-workers[11] described a patient with the Dandy-Walker malformation and syringomyelia. Whitten and colleagues[10] also described a case in which there was "moderate hydromyelia" of the cord. Gardner and coworkers described a proposed mechanism for extension of the increased pressure in the fourth ventricle down the central canal to produce the syrinx. We have recently treated an adult woman who had coexistence of the Dandy-Walker malformation and hydromyelia, as well as another adult woman without hydromyelia. The important clinical features of these interesting patients will be described.

Case Reports

Case 1

This 25-year-old woman was referred to the Mayo Clinic in 1967 because of a convulsive disorder and headaches.

History

She had been born prematurely (birth weight, 2 lb, 13 oz). The anterior fontanelle did not close for several years. She had been treated for arrested hydrocephalus by other medical groups. At the age of 12 or 13 years she began having spells of unconsciousness or of lightheadedness with only a stare. These were controlled by anticonvulsive medications until age 19. Seizures recurred in one to two months with episodes of feeling faint, followed by unconsciousness, mainly nocturnal. Adjustment of anticonvulsant dosage controlled the spells reasonably well until age 24 and the birth of her first child. Suboccipital headaches began a few weeks after delivery, associated with a staggering gait, memory deficit, fatigue, and drowsiness (medications: diphenylhydantoin, 100 mg/day; phenobarbital, 30 mg/day).

Findings on Admission (June 1967)

She was walking with a broad base, was ataxic, and had inequality of reflexes in arms and legs, but there were no Babinski's signs. Pain and temperature were diminished in the right lower extremity.

An electroencephalogram showed left temporal spiking focus and dysrhythmia (grade 2) in the anterior head regions (mu and sleep records). The roentgenogram of the skull was reported as hydrocephalic with enlarged posterior fossa of the Dandy-Walker type (Figure 1).



Fig. 1 (Case 1)—Lateral view of skull, showing marked enlargement and erosion of posterior fossa (Dandy-Walker malformation).

On a fractional pneumoencephalogram, the cerebellar tonsils were long and flat, extending to C-2; no air was in the ventricular system (Figure 2). This was interpreted as probably Arnold-Chiari malformation with marked hydrocephalus. The cerebrospinal fluid protein content was 25 mg/100 ml, with 2 lymphocytes/cu mm.

Operation

Treatment was suboccipital craniectomy with removal of the arch of the atlas and decompression of the foramen magnum (the arachnoid was not opened because of the upright position).

Course

Postoperatively the patient was relieved of headaches. She continued on anticonvulsant medication with no apparent progression until January 1968 when, while clos-



Fig. 2 (Case 1)—Pneumoencephalogram, showing obstruction at C-2 by herniated cerebellar tonsils *(arrow)*.

ing a garage door, she suddenly experienced backache in the mid-dorsal and lumbar regions and noted weakness of the right leg and a right foot drop.

On reexamination in January 1968, pain and temperature sensations were diminished on the right side only to T-4. There was right lower extremity weakness, L-4 to S-1 (−2 to −3). Reflexes were diminished to absent in both upper extremities and markedly diminished in the right lower extremity (knee jerk, −4; Achilles, −2); the left lower extremity reflexes were normal to +1. Because of the peroneal nerve paralysis on the right side and the back pain, myelography (Pantopaque) was done and showed syringomyelia to T-7 and complete obstruction at C-1 (Figure 3). There was no evidence of a lumbar or thoracic lesion other than this. Cerebrospinal fluid protein level was 23 mg/100 ml with 3 lymphocytes/cu mm. Reexploration of the posterior fossa revealed advanced Dandy-Walker malformation. The membrane was removed and the central canal was plugged at the obex with muscle. Postoperatively it was necessary to aspirate large amounts of air and refill the hydrocephalic ventricles with equal amounts of sterile fluids (Figure 4). The convalescent period was prolonged, but after two months the foot drop improved and there was no backache or headache.

By July 1968 (six months postoperatively) the patient



Fig. 3 (Case 1)—Myelograms. *(A)* Normal in lower lumbar area (anteroposterior view). *(B)* Three-quarter view. *(C)* Obstruction at C-1. *(D)* View of cervical and thoracic regions, showing syringomyelia to D-7.

was doing her own housework and caring for her two-year-old child. She had had no major seizures but was maintained on anticonvulsant therapy. Normal menstrual periods returned. Her walking was as good as ever (always with some imbalance, however).

Neurologic examination in October 1968 revealed marked improvement. There was no foot drop, the sensory changes had disappeared, and the preoperative symptoms were absent. The patient was advised to continue with anticonvulsant drugs and to live a normal life but to be careful about any activity that might injure her head or neck.



maintained on anticonvulsant therapy. Normal menstrual

Fig. 4 (Case 1)—Postoperative pneumoencephalogram, revealing extensive hydrocephalus and high tentorial attachment.

Case 2

This 17-year-old white woman presented with a chief complaint of stiff neck, eye pains, and popping in her ears.

History

Her birth, growth and development, family history, and medical history were all unremarkable. She had been well and attending high school until seven months prior to admission, when she began to have pounding bitemporal headaches. Three months prior to admission she had been hospitalized for a flu syndrome, following which she had had a seizure and a sensation of loss of balance. She was rehospitalized and treated with antibiotics. She had recovered from this, but loss of balance and stiff neck continued to be a problem. One month prior to admission she began to have diplopia, sharp eye pains, a feeling of fullness in her ears, and spasms of the biceps and jaw muscles.

Findings on Admission

Her head was of normal size and shape, and she appeared to be a small, normal, teenage girl. Paresis of the left lateral rectus muscle and bilateral nystagmus at end gaze were noted. She had no weakness, but the deep tendon reflexes were generally hyperactive. Babinski's signs were present bilaterally. Her gait was wide-based and unsteady, and neck motions were limited by pain. The laboratory studies gave normal results, but the skull films revealed a large posterior fossa typical of the Dandy-Walker syndrome (Figure 5A). This was confirmed by a brain scan showing elevated lateral sinuses and a right retrograde brachial angiogram showing vessels stretched over the massive fourth ventricle (Figure 5B).

Operation

Following right frontal horn ventriculostomy, suboccipital craniectomy in the upright position was performed and a large cyst wall was exposed. This was opened, revealing that the floor of the fourth ventricle formed the floor of the cyst. Very small, laterally placed cerebellar hemispheres were visible, but the vermis was

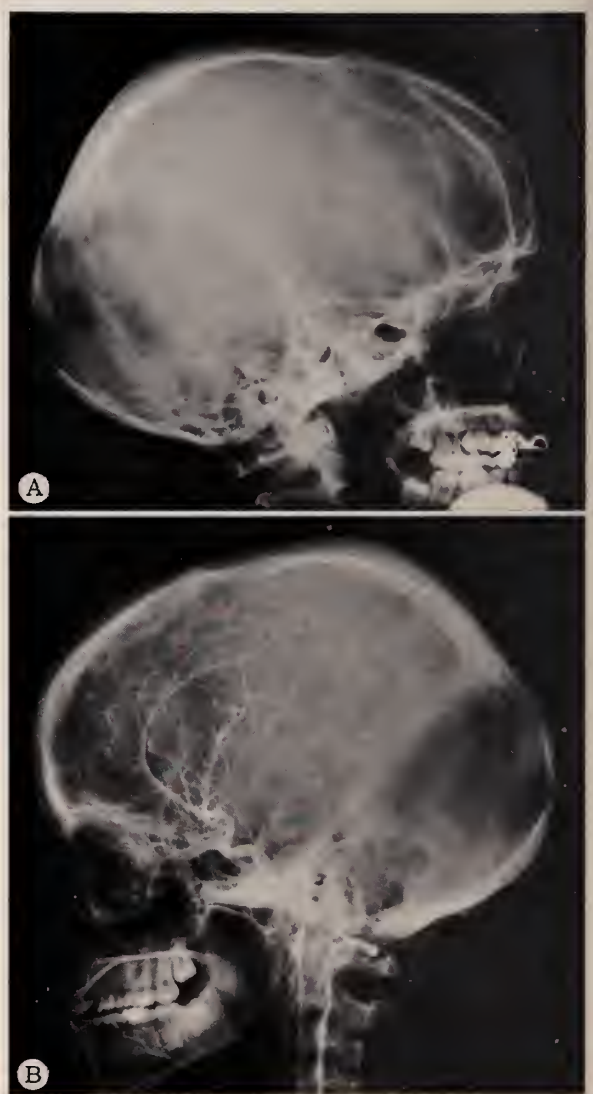


Fig. 5 (Case 2)—*(A)* Lateral skull roentgenogram, showing enlargement and erosion of posterior fossa (Dandy-Walker malformation). *(B)* Right retrograde brachial arteriogram, showing flattening of basilar artery along clivus and stretching of vessels of carotid system, due to hydrocephalus.

absent. A very large aqueduct admitted a rubber catheter. Lateral openings were made in the cyst wall and a large section of the posterior cyst wall was resected.

Course

The patient had a stormy postoperative course marked by aseptic meningitis requiring many lumbar punctures to remove blood from the cerebrospinal fluid. Initially lethargic, she steadily became more alert in the first four postoperative days. She had "spike" fevers daily for three weeks. An episode of acute hemolysis required blood transfusion. When she was dismissed, one month postoperatively, she had headache, left sixth cranial nerve palsy, and some nystagmus; she was walking but somewhat unsteadily.

When seen at follow-up nine months later she had resumed most of her previous activities but still had some headache (Figure 6). The neurologic signs had improved remarkably.

Summary

Two adult female patients with the Dandy-Walker malformation are described, one with associated syringomyelia. The roentgenographic appearance of the skull may be helpful in diagnosis, but the myelogram or encephalogram is often not reliable. The face-down cerebellar position for operation is tolerated best when a large cystic cavity is expected in the posterior fossa; and plugging of the central canal with muscle has been beneficial when syringomyelia is present.



Fig. 6 (Case 2)—Postoperative roentgenograms (9 months). *(A)* Lateral view. *(B)* Note defect in occipital bone and decompression of foramen magnum.

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Rain

If I were running the world I would have it rain only between 2 and 5 a.m.—anyone who was out then ought to get wet.—William Lyon Phelps

Didactic-Preclinical

Development of the Pulmonary Airways

EDWARD A. BOYDEN, Ph.D. (Med. Sc.)*

As an emeritus member of the Department of Anatomy at Minnesota the writer recalls with pleasure the interchange of ideas that developed over a long period between a teaching anatomist and his clinical colleagues at the University of Minnesota. Stimulated by conferences with Dr. Wangensteen and his active group of young surgeons, the anatomist became aware of how little was then known about the gross internal structure of the lungs—information that would guide a surgeon in resecting bronchopulmonary segments or assist a radiologist in locating an obscurely placed lesion. With the aid of younger colleagues it took seven years to clarify this neglected anatomical region.[1]

In the course of this study the clue to variations in the segments was revealed by the exquisite dissections of young human embryos made by Professor L. J. Wells.[2] Bronchopulmonary segments develop from epithelial buds that arise on lobar divisions of the primitive lung sacs. As the lung grows these buds press against the pleura, giving the external surfaces a scalloped appearance. If one of these developing buds escapes genetic control and arises at an atypical spot on the developing bronchi, it causes rearrangement of the pattern of arteries and veins as well as that of the airways.

Considering the fact that "budding" is also the mode of growth in early fetal stages—continuing until the end of the fourth lunar month, during which "pseudo-glandular period" the organ does resemble a gland,[3] it is not surprising that anatomists concluded that budding was the method by which the lung continued to grow after birth.[4,5] But if this were so, the total number of generations of branchings should increase postnatally. Such proved to be questionable, however, in the dog lung. While waiting to collect infant material, the writer found that in puppies 10½ days old (Figure 16 of that article)[6] eight generations of peripheral branches proximal to the original three had developed shallow alveoli without apparently increasing the total number of generations. Rather than "budding" he was witnessing a rapid process of alveolization proceeding in a centripetal direction.

Canalicular Period

In human development it has long been known that the first respiratory tissue appears in lungs between the fourth and sixth fetal month of age. Accordingly, this is called the "canalicular period" since it results in the formation of primitive respiratory "canaliculae."[3] The process is limited to the last three generations of branchings in a total of 12-25, the count depending on the segment involved. In these terminal twigs the cuboidal epithelium becomes pale and attenuated; vascular plexuses develop at its base, and epithelial cells "drop out," apparently permitting underlying capillaries to "surface" upon the air spaces. Indeed,



Fig. 1—Wax reconstruction of "Blue" cluster of respiratory saccules in a "premature" of 30-32 weeks as seen against the pleura (X 100) (Figure 4 in Amer J Anat 126:39, 1969[10]). For view of this model from above, see Figure 5 of same article.

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until F. N. Low's pioneer studies of the lung under the electron microscope,[8] many thought that the original entodermal lining of the lung had disappeared, exposing the air to mesodermal tissue. Early in this important period surfactant appears[9]: the lipoprotein that reduces the surface tension in the air-liquid interface at birth.

Terminal Sac Period

The succeeding period, from the sixth month to birth, is now called the *Terminal Sac Period:* so named because the bronchioles end in clusters of saccules. Only recently have these terminal sprays been reconstructed so that one could analyze the peripheral pattern of airways.[10] A model of such a cluster, in a fetus of 30-32 weeks (1300 grams), is shown in Figures 1 and 1A. The cluster lies next to the pleura and covers an area 0.87 x 0.65 x 0.40 mm. If cuboidal in shape, it would have an estimated volume of less than 0.25 cubic mm. Its branching pattern is as follows: R^3a (in Figure 1A) represents the third generation of smooth respiratory bronchioles. It is lined by flat epithelium on one side and has cuboidal cells on the other. At its end it divides into two short transitional ducts *(4a* and *4b),* both lined by flat epithelium. Each of these ducts gives rise to two clusters of saccules (identified here as "Red" and "Purple," "Yellow" and "Blue"). The "Blue" one begins with ramus *5'a.* Note that the cluster has four to five generations of saccules, several of which are trifurcate. Figure 3 is a photomicrograph of an adjacent area showing the saccules, a vein (*V*) and lymphatics (*L*).

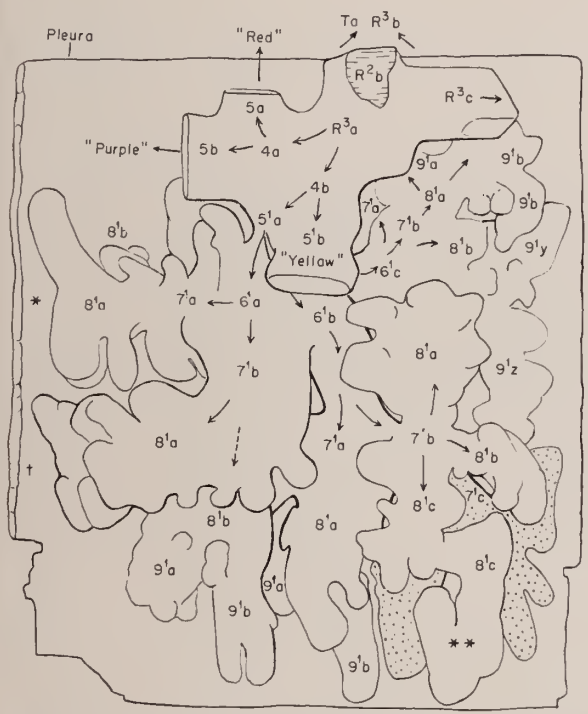


Fig. 1A—Analysis of branching pattern (Figure 4A from above article). The stem of the Blue clusters (*5'a*) trifurcates into *6'a, 6'b* and *6'c.* Ramus *6'a* divides into *7'a* and *7'b.* The upper branch of each is of peculiar shape; the one indicated by an asterisk is depressed, then gives off cylindrical processes from upper and lower borders. The lower *8'a* (indicated by a dagger) bends sharply at right angles. Ramus *6'b* trifurcates into *7'a, b, c.* Its branch *7'b* then trifurcates. **, a recurrent branch of *8'c.*

This premature infant lived 19¼ hours and had two cyanotic attacks (not very severe), from the last of which it died. Note that the saccules are lined by flat epithelium (*P.E.*, Figure 2) and that fetal connective tissue intervenes between adjacent air surfaces which, in turn, are underlined by capillaries (*C*). Flecks of proteinaceous material are indicated by arrows. As noted previously, no alveoli are present in this terminal sac period, but elastic and collagenous bundles of connective tissue are being formed which will serve as anchor points (*Figure 2), between which growth of alveoli will eventually occur.[11] At term, alveoli are present, but small and shallow.

Such is the pulmonary apparatus with which the infant is born.

Postnatal Changes

The postnatal changes are equally impressive. Since these will be summarized at greater length in a forthcoming issue of the Brennemann-Kelley *Practice of Pediatrics,* it must suffice here to mention only the salient points.

As in the puppy, alveolization proceeds centralwards from the periphery—first along the saccules, then successively along alveolar ducts, respiratory and terminal bronchioles.[12] At higher levels and in later stages, alveoli arise as balloon-like expansions of diverticula initially lined by columnar cells.[13] By the eighth year all alveoli will have been formed, after which the lung grows merely in size.[14] Collateral ventilation develops in three ways: by pores of Kohn connecting contiguous alveoli, by the formation of "Lambert ducts" between subterminal bronchioles and adjacent alveoli,[13] and by anastomoses between adjoining acini.[15]

Clinically, two problems stand out above all others: (1) the *Respiratory Distress Syndrome,**

*See Chapter 8 in E. M. Scarpelli's: The Surfactant System of the Lung. Lea & Febiger, Philadelphia, 1968.

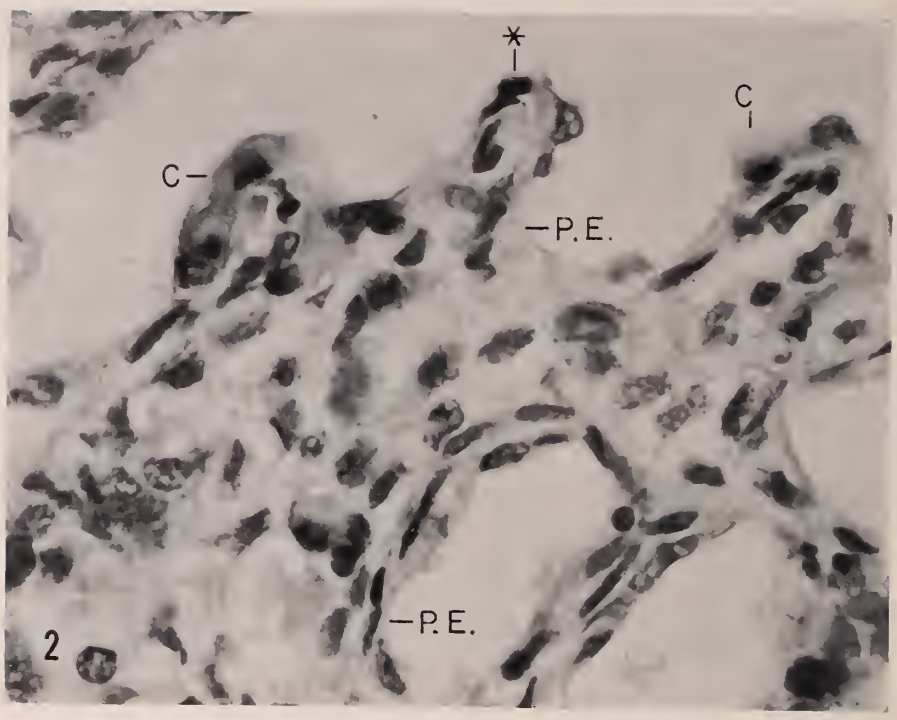


Fig. 2—Photomicrograph of section 28d (X 120) showing bold protrusion of capillaries (C) into lumen of saccules (Figure 6 in Am J Anat 126:39, 1969[10]). *P.E.*, pulmonary epithelium: *asterisk*, knotted protuberance suggesting presence of elastic tissue.

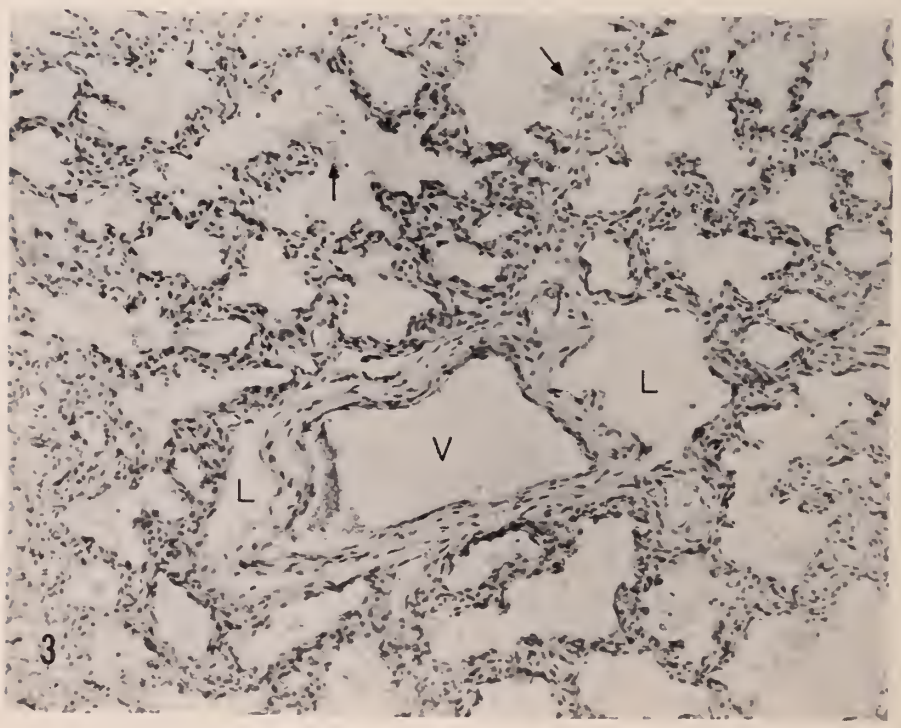


Fig. 3—Photomicrograph of section 27d (X 83) showing enlarged lymphocytes (L), a vein (V) and the presence of proteinaceous material (arrows) in the saccules (Figure 7 in Am J Anat 126:39, 1969[10]).

involving initial insufflation of the newborn lung and (2) the *Obstructive Pulmonary Syndrome*.[16] Complicating our understanding of the airways has been an almost complete ignorance of the specific structure of the terminal respiratory unit, the pulmonary acinus. This is a terminal bronchiole and all its branches. Recently it has been estimated that there are some 80,000 of them.[15] In the lung of a child, age 6⅔ years, an acinus has a volume of some 15 cubic mm. If it were shaped like a cube, it would measure about 2.5 mm on each side. By reconstructing it and using the formula $T = X^2/D$ [where X is the distance in centimeters and D (0.2) is the diffusion constant for respiratory gases] one may estimate that it would take 0.4 seconds for half the CO_2 to diffuse out from the end of the acinus to the terminal bronchiole, a distance of 3.95 mm.[15]

From this brief survey it would appear that the lung is still one of the most challenging areas for research.

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Thanksgiving

The first Thanksgiving Proclamation was made by Governor Bradford three years after the Pilgrims settled at Plymouth:

"To all ye Pilgrims:

"Inasmuch as the great Father has given us this year an abundant harvest of Indian corn, wheat, peas, beans, squashes, and garden vegetables, and has made the forests to abound with game and the sea with fish and clams, and inasmuch as He has protected us from the ravages of the savages, has spared us from pestilence and disease, has granted us freedom to worship God according to the dictates of our own conscience; now I, your magistrate, do proclaim that all ye Pilgrims with your wives and ye little ones, do gather at ye meeting house, on ye hill, between the hours of 9 and 12 in the day time, on Thursday, November ye 29th, of the year of our Lord one thousand six hundred and twenty-three, and the third year since ye Pilgrims landed on ye Pilgrim Rock, there to listen to ye pastor and render thanksgiving to ye Almighty God for his blessings.

—William Bradford, Ye Governor of Ye Colony."

Didactic-Clinical

Urinary-Vaginal Fistulas

JOSE C. PACHECO, M.D.* AND JOSEPH H. PRATT, M.D.†

URINARY-VAGINAL FISTULAS have been an inherent complication of parturition and malignancy through the ages. The Egyptian Mahfouz[1] has reported Derry's description of a vesicovaginal fistula in a mummy about 4,000 years old. Because of inadequate and often traumatic obstetric care, childbirth has been the leading cause of vesicovaginal fistulas. It was considered that prolonged pressure of the fetal head on the symphysis pubis during the second stage could devitalize the vesicovaginal septum, while difficult forceps delivery could directly traumatize the septum. McConnachie[2] stated the belief that during labor the bladder is in an intra-abdominal position. It is only when the bladder base is attached to the lower uterine segment that, with the retraction of the latter, the bladder base suffers undue stretching. This impairs its blood supply and predisposes to the formation of fistula.

Causes of Fistula

Obstetric Trauma

In 1920, Judd[3] reviewed the cases of urinary-vaginal fistula repaired during the previous decade at the Mayo Clinic and found that 39% were related to obstetric trauma. Better evaluation of the pelvic perimeters, more awareness of dystocia, careful supervision of trials of labor, and proper indications for forceps deliveries, episiotomy, and cesarean sections have considerably reduced the incidence of obstetric injury in modern times. In 1964, Massee and associates[4] reported that of the urinary-vaginal fistulas treated at the Mayo Clinic in the previous decade, only 5.7% occurred after childbirth trauma. This cause was responsible for 18.8% of the cases reported by Everett and Mattingly[5] in 1956 and for 14.7% of the cases of Miller and George[6] in 1954. But Louw,[7] Coetzee and Lithgow,[8] and Longo,[9] from South Africa and Nigeria, respectively, reported that about 80% of the urinary-vaginal fistulas treated in these places were secondary to obstetric trauma.

Pelvic Operations

In recent years in most medical centers, trauma during pelvic operations has become the leading cause of fistula formation. Massee and his coworkers[4] found that in about 80% of 262 patients the fistulas occurred postoperatively, 153 of these after abdominal hysterectomy. Other fistulas occurred after excision of the cervical stump, plastic vaginal operations, vaginal hysterectomy, radical hysterectomy, and vesical-neck resection. Interruption of the blood supply, technical difficulties, distortion of the anatomy, and vascular changes after irradiation are factors in the formation of the fistulas.

Malignancy

Malignancy can lead to the formation of urinary-vaginal fistulas, either directly by necrosis or infection, or indirectly by surgical and radiotherapeutic procedures. Everett and Mattingly[5] reported 46 cases of vesicovaginal fistula associated with carcinoma of the cervix. All but three of the patients had been irradiated. Forty-four urinary-vaginal fistulas occurred after the Schauta-Amreich vaginal operation in 1,000 cases reported by Inguilla and Cosmi,[10] and these fistulas occurred from a few days to 13 years or more postoperatively. [Treatment of cancer in 10 of the 262 fistula cases at the Mayo Clinic was only by pelvic radiation.] Counseller and Welch[11] found a relationship between the interval of onset of urinary drainage after the surgical procedure and the type of injury sustained. If a defect occurred in the urinary tract, the patient might pass urine through the vagina during the immediate postoperative period. If the urinary drainage appeared about a week after the operation, it was most likely due to suture material in or around the wall of the bladder or ureter. If the fistula appeared after two

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weeks, it was most probably related to pressure necrosis, as from a hematoma or pack or ischemic sloughing.

Symptomatology

Incontinence

The primary symptom of an established urinary-vaginal fistula is, of course, urinary incontinence.

The incontinence of urine may be slight in patients with small fistulas, and these patients may void adequately, making the diagnosis difficult. Patients with large fistulas cannot retain any urine in the bladder.

Inflammatory Reaction

Urinary incontinence may evoke an inflammatory reaction of the vagina, vulva, and thighs, and if there is a breakdown of the urine, there will be a collection of urinary salts, excoriation of tissues, the formation of furunculosis, and a most disagreeable odor.

During the formation of the fistula, the patient usually complains of frequency, dysuria, and urgency of urination and may have a low-grade fever for a few days. Urinalysis shows both leukocytes and erythrocytes. When the fistula occurs after obstetric or surgical trauma, these symptoms will last a few days and then incontinence will follow. But when the fistula results from irradiation, the symptoms of fever, malaise, and weight loss, resembling carcinoma, may persist for several months. Once a fistula is established, the general condition of the patient rapidly improves.

Diagnosis

When the fistula is large, it can be seen with adequate exposure or can be palpated through the vagina, but the diagnosis of small fistulas will have to be differentiated from incontinence due to weakness of the sphincter. Spurts of urine from the meatus produced by coughing or straining will denote a partially incompetent sphincter.

Indigo Carmine

Indigo carmine injected intravenously will be promptly eliminated through the urinary system, and the inner end of a sponge or pack placed in the vagina will be stained a bluish green when a urinary fistula exists above the vesical neck.

Urogram

After the existence of a urinary fistula has been proved, the next step is establishing the anatomic location. With vesicovaginal fistulas, the urogram is usually normal, unless the ureteral orifices have been involved by an inflammatory reaction. On rare occasions, the vagina will be outlined by the contrast material, and the site of the fistula also will be evident. During cystoscopy, methylene blue or indigo carmine can be instilled into the bladder, and its appearance in the vagina also will demonstrate the presence and site of a vesicovaginal fistula.

Seton

A point of great surgical help and expediency, when possible, is to pass a thread of silk through the fistula and leave it as a guide for the surgeon. To accomplish this, at cystoscopy a flexible ureteral catheter is passed through the fistula into the vagina, the end of a piece of silk is tied to the tip of the catheter, the catheter is withdrawn, and the free ends of the silk (one coming out of the urethra and the other from the vagina) are loosely tied together and left as a guide and possible retractor at surgery.

Ureterovaginal

The patient with ureterovaginal fistula will experience incontinence, but at the same time she preserves normal micturition. The excretory urogram usually, but not always, shows ureteral ectasia above the fistula due to narrowing and obstruction by fibrosis at the affected site. Some contrast material may be seen passing through into the vagina. Cystoscopic findings are within normal limits, but the orifice of the compromised ureter may show little or no urine. Ureteral catheterization reveals obstruction in at least 90% of the cases.[12]

Urethrovaginal

The symptoms in urethrovaginal fistula situated near the vesical neck are similar to those in vesicovaginal fistula. But if such a fistula is near the meatus, urine will escape only during micturition and repair is optional.

It is most important to remember that fistulas may be multiple, and the possibility of a second fistula should always be excluded before the repair of a known fistula is attempted.

Preoperative Treatment

Supportive Measures

A minimum of three months should elapse between the fistula formation and an attempt at repair. During this time, supportive measures for improvement of the local tissue are advised. This includes adequate nutrition, treatment of urinary infections, local or systemic administration of estrogens in menopausal women, short-wave diathermy to soften and revascularize the scar tissue, and hot sitz baths. Collins and associates[13] have reported success in the early repair of urinary-vaginal fistulas with the preoperative use of cortisone (100 mg three times a day for 10 days). This method has not been used at the Mayo Clinic.

When a traumatic fistula is seen a few days after its formation, and if the fistula is clean and the surrounding tissues are healthy and not very edematous, immediate closure can be attempted and may be successful.

Local Cautery

Occasionally, small fistulas do heal spontaneously. If epithelization seems to be occurring along the fistula tract, this can be stopped with local applications of a 5% silver nitrate or tincture of iodine, or careful and delicate electrocoagulation.

Fistulas occurring after previous attempts at repair have to be evaluated and observed for longer periods, so that the tissues have a chance to return to a more normal condition.

Surgical Repair of Vesicovaginal Fistula

The approach for surgical repair depends on the type of fistula and the condition of the tissues.

The fistula most frequently seen, the vesicovaginal fistula, may be repaired either vaginally or suprapubically, the gynecologist generally preferring the vaginal route. In any case, good visualization and good illumination are necessary. For vaginal repairs, Kraske's position (modified knee-chest position) has been used extensively, but now the lithotomy position is preferred. Good retraction is necessary to expose the fistula.

A Schuchardt incision will be helpful when the vagina is narrow or atrophic.

An elliptical incision is made around the fistulous opening, and the vaginal mucosa is freed for one to three cm about the fistula. Blunt dissection with the finger beneath the vaginal mucosa may help to mobilize the bladder, allowing it to be pulled forward. The bladder can be further mobilized by opening the cul-de-sac and freeing the bladder base. Then the scar tissue around the fistula is excised, all the scar tissue being removed until healthy tissues are encountered.

Closure of the defect is accomplished by using two or three transverse rows of fine absorbable sutures, each row extending one cm beyond the former one. The bladder mucosa should not be included in the sutures, and the tissues should not be under any tension. This latter is probably the single most important point. If there is tension on the suture lines additional mobilization of the bladder will be necessary. Finally, the vaginal mucosa is closed with interrupted sutures, preferably in a different plane so that all of the suture rows do not overlap.

Other Techniques

Not all fistulas can be closed with the same technique, and the surgeon will have to choose the appropriate one in each individual case. Other suitable techniques are those of Latzko's high colpocleisis, the Sims-Simon extensive scar-tissue excision, and the Mayo-Fueth fistula-inversion operation. When the tissues show poor vascularization, interposition of the bulbocavernosus or of the gracilis muscle, or even of the uterine fundus, may be necessary.

Urologists prefer the transvesical approach for repair of the fistula. A suprapubic cystotomy is performed, the scar tissue around the fistulous tract is removed, and after mobilization of the bladder from the vagina, the vaginal wall and the bladder wall are closed in separate layers.

Transperitoneal Approach

If the vesicovaginal fistula is high, or if other surgical procedures within the pelvis are necessary, the transperitoneal approach is advisable.

Martius-Harris Operation

In the rare cases in which the urethra is practically destroyed, urethroplasty is advised after either the Martius-Harris operation when the roof of the urethra is intact or the Everett-Te Linde operation when the complete urethra is destroyed.

Repair of Vesicouterine Fistula

Vesicocervical and vesicouterine fistulas also

can be repaired with the patient in the lithotomy position. After the bladder is completely mobilized from the uterus or cervix, the fistula is repaired as for a vesicovaginal fistula, and the defect in the uterus or cervix is closed. An abdominal approach may be necessary for the vesicouterine-vaginal fistula if there is a stenotic vagina or severe fixation of tissues.

Repair of Ureterovaginal Fistula

When a ureterovaginal fistula is discovered early after operation, ureteral catheterization should be attempted. This may result in spontaneous healing in 10 to 14 days. But this situation is unusual. Most ureterovaginal fistulas are discovered or, in many cases, develop after the patient has been dismissed from the hospital. This delayed formation is due to a gradual necrosis from an impairment of the blood supply as a result of operation, or by radiation effects. The repair of the fistula will differ according to the condition of the ureter and of the kidney on the involved side. Rarely, the segment of the ureter with the fistula can be excised and a ureteroureteral anastomosis done. There must be no tension on the anastomosis. To prevent stricture of the anastomosis, an oblique, a fishmouth, or a Z-plasty anastomosis is best. Usually, such an operation cannot be accomplished, and the ureter has to be reimplanted into the bladder. The reimplantation should be made in the most adjacent portion of the bladder as feasible to reduce tension. When the terminal ureter is damaged owing to previous radionecrosis, or the fistula is high, or a longer segment has to be excised, construction of a tube with a bladder flap or interposition of a segment of ileum will be necessary to reestablish continuity. All ureteral anastomoses should be drained, because if there is further leakage and urine collects around the anastomosis, fibrosis will inevitably result.

Urinary Diversion

Urinary diversion is employed when there are large, inoperable, low-urinary-tract vaginal fistulas, or when there is extensive scarring of the pelvic ureters due to prior surgery or radiation, or as a palliative measure for malignant fistulas. Bilateral nephrostomy may be necessary as an emergency procedure. Then the choice of permanent urinary diversion is made according to the condition of the patient or her life expectancy. Ileal conduit procedures have gradually replaced ureterocolonic operations, though, in a recent paper, Symmonds[14] stated that ureterosigmoidostomy or a rectal reservoir is still a reasonable procedure if the patient's life expectancy is short or if her condition is precarious.

For the ileal conduit, a segment of ileum about eight cm long and about 10 cm from the ileocecal valve is isolated, with preservation of its mesentery. The ureters are mobilized with conservation of their periureteral connective tissue. The left ureter is brought medially through an opening in the base of the mesentery of the sigmoid. Both ureters are brought under the segment of ileum, and then curved upward to its anterior aspect, where they are anastomosed near its proximal end. The distal end is then delivered through a circular incision and secured, mucosa to skin, in the right lower quadrant. Brunschwig and Barber[15] advise the mobilization of the cecum mesially, after which the conduit is passed under it, previous to its attachment to the opening in the abdominal wall. A segment of sigmoid colon may be used as a conduit equally effectively, and if exenteration is done it requires one less anastomosis.

In patients with bilateral ureteral lesions and a hypotrophic and fixed bladder, side-to-side or end-to-side anastomosis of an isolated ileal segment to the bladder and implantation of the ureters to the segment have been performed.

Postoperative Care

Keep Bladder Empty

The bladder has to be kept empty, and the indwelling catheter has to be free of blood clots and other obstructive materials. The catheter is irrigated frequently with normal sodium chloride solution during the first 24 to 48 hours. Orally administered sulfa drugs or a urinary antibiotic, acid-ash diet, and urinary acidifiers are used routinely. The urine is maintained at a pH of 5 to 5.5. Vaginal examinations are prohibited for at least three weeks, and coitus is not permitted for three months.

Prevent Ascending Infection

In the cases of urinary-tract diversion, ascending infection has to be prevented with adequate use of antimicrobial therapy. And, particularly when the ureters have been implanted into the colon or a rectal bladder has been established,

hyperchloremic acidosis has to be considered as a possible complication. In this condition, the blood chloride level is elevated, CO_2 combining power is reduced, and blood urea nitrogen level is increased. Clinically, the patient may present weakness, loss of appetite, nausea, reduced sensorium, and even coma. If the complication is present, rectal tube drainage of the urine, large intake of fluids (four or five liters a day at the beginning), and administration of six to 10 gm of sodium bicarbonate until the CO_2 combining power returns to normal limits are indicated.

Complications

The most frequent postoperative complications are those of cystitis, thrombophlebitis, pulmonary embolism, ureteral obstruction, and ileus. Ascending infection and hyperchloremic acidosis are the most important complications of urinary-tract diversion. The presence of several other complications stresses the importance of close supervision by the physician in the postoperative period, and symptomatic treatment should be given in all cases.

Results

The results depend on several factors, essentially on the cause of the fistula, the condition of the patient, the presence of malignancy, previous irradiation, previous attempts at repair, and on the skill of the surgeon. In a recent report from the Mayo Clinic,[4] the initial attempt at repair was successful in 88% of 262 fistulas. Of the 31 cases of initial failure, subsequent attempts were made in 19 cases, with success in 18. Forty-six patients required excisional or diversional procedures for a successful closure of the fistula.

Prevention of Fistula Formation

Radiation treatment of cancer produces endarteritis in the surrounding tissues; this leads to ischemia of the tissues, sloughing, and scarring, producing a favorable condition for the development of fistulas. Postradiation fistulas are difficult to repair. Hence, the necessity and method of administration of radiotherapy must be carefully evaluated in each individual.

Meticulous Technique

Most particularly there must be a careful, gentle dissection at surgery in the postradiated patient.

Since the great majority of fistulas occur after a "routine" abdominal hysterectomy, the surgeon should know the anatomic relations of the pelvic structures at all times.

Counseller and Haigler,[16] and Symmonds and co-workers[17] have emphasized the advantage of constant traction and countertraction during dissection, for a better exposure of the urinary system. They also stress the importance of visual or palpatory identification of all structures before clamping, cutting, or placing sutures. Special care is necessary in the region of the ovarian and uterine vessels, where injury to the ureter is common, and also at the reflection of the base of the bladder, which can be damaged during its mobilization, or when the cardinal ligaments are sutured to the vaginal vault. Cross-clamping of the vaginal cuff during and after removal of the uterus can easily damage the bladder.

Radical hysterectomy and exenterative procedures always compromise the blood supply of the terminal portion of the ureters to some extent. At the Mayo Clinic in the past 30 years, Welch and Counseller[18] found that urinary fistula occurred after Wertheim hysterectomy in 11.9% of patients having had preoperative irradiation and in 3.2% of those receiving primary surgical treatment.

In an earlier report on extended Wertheim operation, Symmonds and co-workers[19] obtained corresponding figures of 24.2% and 5%. Symmonds and Pratt[20] have found that these figures are lower when there is preservation of the adventitia of the ureter, even though the anterior division of the internal iliac artery or of the entire iliac artery and vein are removed for better exposure. Improved technique of perintonealization of the bladder base, rectum, and lower ureter and use of extraperitoneal suction catheters at both iliac fossae after radical hysterectomy have helped.

Conclusion

During the years, the principal cause of such fistulas has changed from obstetric to operative trauma. The commonest fistula is the vesicovaginal. Its surgical repair is done preferably transvaginally with the patient in the lithotomy position, using a multilayered closure without tension. Closure on the first attempt was accomplished in 88% of 262 patients. There were 31 failures; a second attempt was made in 19 of these cases, with a subsequent cure in 18.

References may be secured from the author or the reprints.

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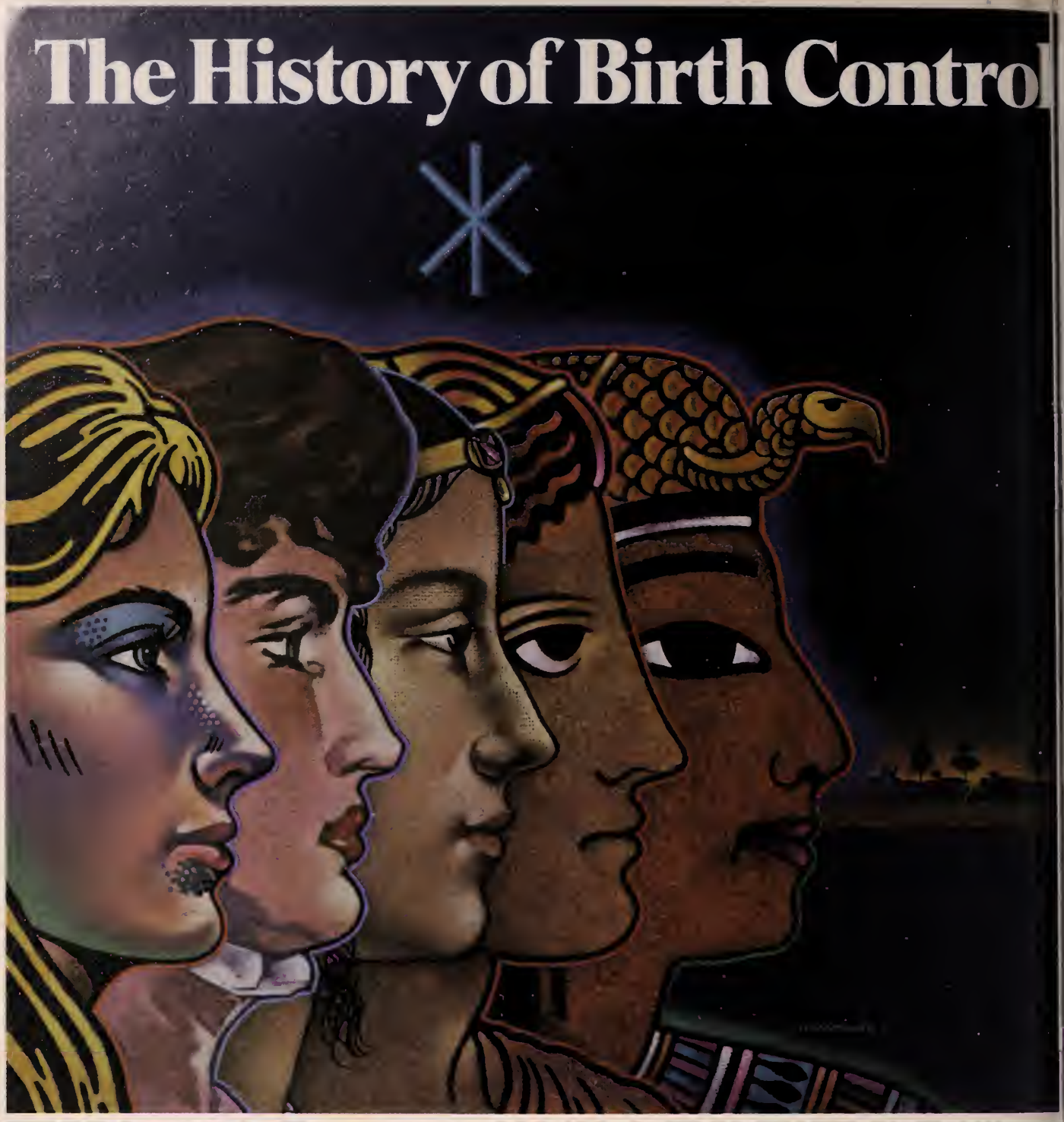
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It may seem now that such advances as oral contraception and the IUD have freed women from this often fruitless search and consequent suffering, but there are millions of women in the United States and elsewhere who have less knowledge of, and less recourse to, contracepti than Egyptian women of the Twelfth Dynasty. Nothing is more urgent to all of us than to bring them help. We cannot long support the ecologic pressures of an additional 70 million Earth inhabitants each year.

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An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication—Ovulen and Demulen are indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality conducted in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study of Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Ovulen and Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Ovulen or Demulen. Therefore, if such tests are abnormal in a patient taking Ovulen or Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen or Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen or Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen or Demulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen or Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

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Editorials

Implications of Hyperlipidemia Associated with Use of Oral Contraceptives

THE OBSERVATION of Johnson and Lee published in *Minnesota Medicine* (May 1971)* and the observations of other investigators[1] regarding hyperlipidemia in patients taking oral contraceptives raise the intriguing question of whether oral contraceptive therapy may be associated with accelerated atherogenesis on the basis of this hyperlipidemia. The usual vascular lesions seen in patients on oral contraceptives have been venous thromboses, but cerebrovascular and cardiovascular disease have also been reported in such patients.[1] A hypercoagulable state with elevated levels of clotting factors has been postulated by some as the mechanism of the vascular disease seen in patients on oral contraceptive drugs. However, a recent national coronary-drug project indicated that the use of Premarin may be associated with an increased incidence of coronary artery disease.[2] Thus by inference one may implicate oral contraceptive therapy in accelerated atherogenesis.

Hypertriglyceridemia may be associated with increased incidence of coronary artery disease, but this is disputed in the absence of elevated levels of cholesterol. It would seem highly unlikely that hypertriglyceridemia and hyperlipoproteinemia over a prolonged time could be innocuous.

The further question arises as to the mechanism for the hyperlipidemia in patients on oral contraceptives. It is well known that the oral contraceptive agents increase such binding proteins as thyroxine-binding globulin and cortisol-binding globulin.[1] Thus it is possible that oral contraceptives stimulate synthesis or decrease degradation, or both, of very low-density lipoproteins either in the liver or in other organs giving rise to hyperlipoproteinemia and hyperlipidemia. Recent work on the structure of apoproteins has indicated that possible derangements of these apoproteins may be associated with such rare diseases as Tangier disease and a-beta-lipoproteinemia.[3,4] It may be that the oral contraceptives increase the formation of low-density apoprotein which leads to an elevation of the lipoproteins followed by an increase in serum lipids; on the other hand, oral contraceptives may interfere with factors that clear triglycerides from the plasma. In addition to these considerations, genetic predisposition of the individuals on oral contraceptive therapy may be a factor, and if genetically predisposed individuals can be identified, the use of oral contraceptives would be contraindicated.

The bits of evidence accumulated to date are not sufficiently reliable to enable us to make firm judgments. Only through further study of formation of lipoprotein under the stimulus of dietary and drug factors can we hope to elucidate

*Johnson, H. W., and Lee, G. B.: Changes in Serum Lipids During Administration of an Oral Contraceptive. Minnesota Med 54: 335, 1971.

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the mechanisms of hyperlipoproteinemia and hyperlipidemia, and only through knowledge of these mechanisms can we attempt to prevent and hopefully correct the vascular disease, primarily coronary artery disease, associated with hyperlipidemia.

Pasquale J. Palumbo, M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation.

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Folate Deficiency, Absolute and Relative*

Folic acid through its coenzyme forms plays an important role in de novo purine and pyrimidine nucleotide biosynthesis and in the interconversion of certain aminoacids.[1] Thus this vitamin becomes important in nucleic acid and protein formation. Folate deficiency is usually due to (1) Poor nutritional intake of this vitamin;[2] (2) Defective absorption, most often acquired,[3] rarely congenital;[4] (3) Increased demand for this vitamin as in pregnancy,[5] hemolytic anemias,[6] hematological malignancies,[7] and rapidly growing tumors;[8] and (4) Excessive loss from the body through urine,[9] sweat,[10] bile,[11] desquamating epithelium[12] or hemodialysis.[13] In all of these conditions the body stores of folates are low. The serum and red blood cell levels as measured by the conventional Lactobacillus casei assay are therefore decreased.

It is more difficult to understand that functional folate deficiency may in fact also exist in the presence of normal or increased serum folate values measured by the same bioassay method. This may occur in vitamin B_{12} deficiency and is best explained by the N^5 methyl tetrahydrofolate "trap" that is believed to exist in B_{12} deficiency.[14] This is due to the fact that the interconversion of homocysteine to methionine is dependent on an enzyme that requires both N^5 methyl tetrahydrofolate alcohol and methylcobalamin for its proper functioning. In the absence of vitamin B_{12} and consequently methylcobalamin, N^5 methyl tetrahydrofolate alcohol cannot be converted to tetrahydrofolate alcohol. Under these circumstances a lack of this reduced form of folic acid and other folate coenzymes derived from tetrahydrofolate alcohol may ensue at the time when N^5 methyl tetrahydrofolate alcohol accumulates. Whether the mammalian cell has an alternate non-B_{12} dependent pathway between homocysteine and methionine[15] as described for bacteria[16] remains to be proved. It is, however, known that some patients with B_{12} deficiency have normal or low serum folate levels,[17] although this might be explained on the basis of poor dietary intake of folate-containing food due to the gastrointestinal upsets that so often accompany pernicious anemia.[18]

Another form of functional folate deficiency occurs with defects in the interconversion of the various folate coenzymes. Several enzymes are involved in this interconversion. Three congenital defects in these enzymes have been described.[19] Although these enzyme deficiences have not been described outside of Japan, this failure may be due to inadequate search for them. The total folate activity in serum of these patients is elevated, whereas a relative lack of one or more of the folate coenzymes is believed to exist because of the enzyme deficiency.

It is of considerable interest that the children with these enzyme abnormalities had mental retardation with organic brain damage; but not all had megaloblastic anemia. In congenital malabsorption of folate, both mental retardation and

*Rowe, P. B.: Inborn Errors of Folic Acid Metabolism—The Regulation of the Interconversion of Active Derivatives of Folic Acid. Minnesota Med 54:391, 1971.

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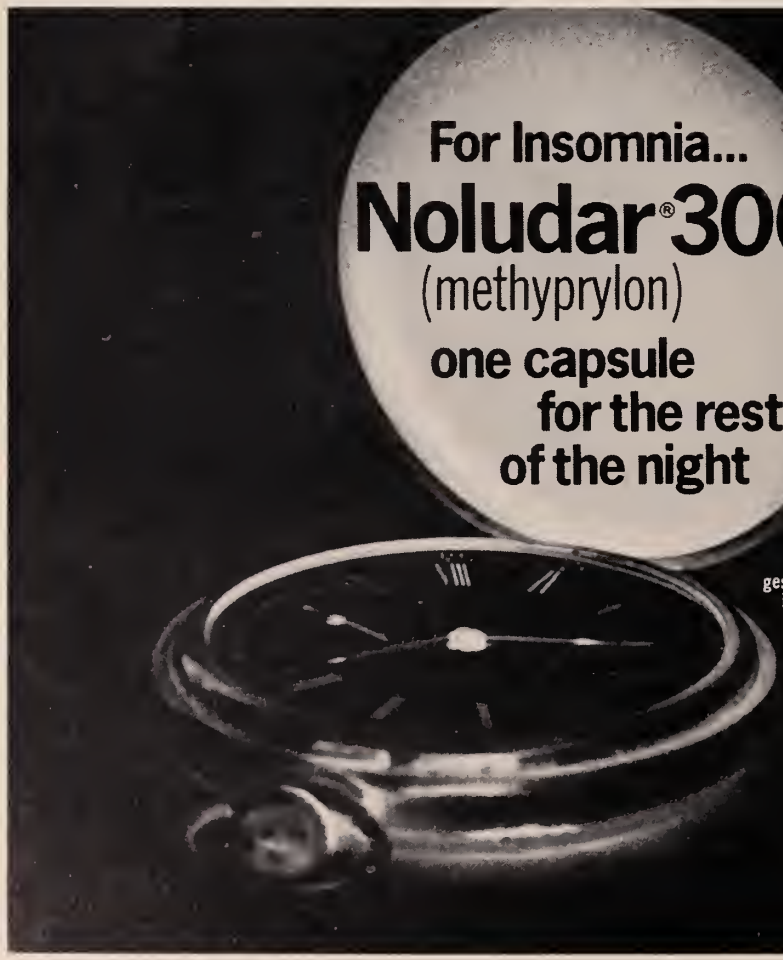


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Usage in Pregnancy: Weigh potential benefits in pregnancy, during lactation, or in women of childbearing age against possible hazards to mother and child.

PRECAUTIONS: If sleeplessness is pain-related, an analgesic should also be prescribed. Perform periodic blood counts if used repeatedly or over prolonged periods. Total daily intake should not exceed 400 mg, as greater amounts do not significantly increase hypnotic benefits.

ADVERSE REACTIONS: At recommended dosages, there have been rare occurrences of morning drowsiness, dizziness, mild to moderate gastric upset (including diarrhea, esophagitis, nausea and vomiting), headache, paradoxical excitation and skin rash. There have been a very few isolated reports of neutropenia and thrombocytopenia; however, the evidence does not establish that these reactions are related to the drug.

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megaloblastosis occur. Thus, both absolute and functional folate deficiency may therefore be deleterious to the young and developing brain. This is in keeping with the findings in the offsprings of folate-deficient rats[20] as well as for infants born to women who have been on a folate-deficient diet[21] or on a folate antagonist during pregnancy.[22] Circumstanial evidence exists only for the importance of an intact folate metabolism for the fully developed brain and nervous system.[23-27]

The regulation of the enzymes active in the interconversion of the various folate coenzymes is a new and promising but very complex field for biochemical research;[28] but its application to clinical medicine is conjectural at the moment. It should not come as a surprise, however, if new and important medical information is obtained by further investigation into the field of folate metabolism and its regulation. The recently discovered 5-methyl-dihydrofolate alcohol found in the blood is a testimony to this effect[29] although its metabolic significance and interrelation are unknown at the moment. It should also be kept in mind that unidentified folate compounds are present in mammalian cells waiting for identification[30] and exploration of their significance.

A. Doscherholmen, M.D.
Minneapolis, Minnesota

References may be secured from the author.

Acute Cholecystitis in Children*

ACUTE CHOLECYSTITIS is relatively uncommon in children. It is this rarity which leads us to ignore the possibility and thereby delay appropriate therapy. The report by Rutledge of a five-year-old boy with acute cholecystitis serves to jog our thinking on this subject. While we are familiar with cholecystitis and cholelithiasis associated with hemolytic disease, we are less experienced with acute cholecystitis when it follows a systemic illness—or, as in the case reported, there is no history of predisposing circumstances. It has been pointed out that acute systemic illness may provide the predisposing factor of bile stasis, so often incriminated in acute cholecystitis, by virtue of dehydration from inadequate fluid intake, administration of drugs to relieve pain, and decreased hormonal stimulation of the gallbladder.

A comparison of this condition in children and in adults reveals several important points.

1. Acute systemic febrile illness plays a more prominent and more frequent role in children.

2. Sex incidence in children is different (3:2, males predominating, in most published reports of cases in children).

3. Children have a higher incidence of recent jaundice but a much lower incidence of common duct stones as well as gallbladder stones.

4. Histopathologic changes in children are more typically the acute inflammatory type; there is more frequent evidence of malformation of the cystic duct in cases in children.

5. Surgical treatment is equally satisfactory in both age groups, but there is much less indication to explore the common duct in children.

A recent report by Woolley from the Los Angeles Children's Hospital described 33 cases in patients less than 17 years of age during the past 20 years. The most disquieting feature of this report is the fact that 15 of these cases have been encountered in the last three years. It has been reported in children as young as 17 days, by Arnspiger, and six weeks, by Wolley. Our youngest patient was three years old. We may be forced to search for additional factors associated with our modern way of life which can be contributing to this condition.

The important point to gain from Rutledge's presentation is the fact that an acute abdomen should be treated promptly and correctly even if the exact etiology is obscure.

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Rochester, Minnesota

*Rutledge, J. B.: Acute Cholecystitis in a Child. Minnesota Med 54: 757, 1971.

†Mayo Clinic and Mayo Foundation.

The alienist is not a joke:
He finds you cracked, and leaves you broke.—Keith Preston

Drugs. Physicians. and the "Medical Model"*

That the problems of drug abuse and addiction continue to challenge our profession is well emphasized by Maslansky in his review of Opiate Addiction in Minnesota. The variety of addict "types," the psychophysiologic aspects of addiction, the fallacy of the "seller-user" dichotomy, the need for realistic treatment goals implying a flexible therapeutic approach, and the origins of chemical dependency in peer-sanctioned alcoholic behavior are all valid points appropriately made. As the author indicates, no accurate count of addicts has been made nor, for that matter, *can* be made under the existing medical-legal umbrella. We do know more reliably, however, the extent of alcoholism, a common "addiction" (or as the World Health Organization currently classifies addictions, a "drug dependence"). Conservative estimates place the incidence of alcoholism at 3% to 4% of our general population. Dr. Roger Egeberg has stated before a Senate subcommittee that there are somewhere between 4.5 and 6 million alcoholics in this country, and most of them are not getting the care they need.

Perhaps we physicians can learn from our rather dismal record in the field of alcoholism that we must not carry over similar attitudes to the broader problem of drug dependence. For reasons only partly understood we have been reluctant to assume responsible roles in treating the alcoholic. Some obvious explanations for our hesitancy are the absence of realistic training experiences with alcoholics (physicians usually are exposed only to the complications of this illness); a pervasive feeling of therapeutic pessimism, if not nihilism, based upon our observations of alcoholism as a chronic relapsing condition; and, of utmost importance, the conceptual model still held by many physicians that alcoholism is not a true "disease," or that it may be just a "bad habit," or that it must be a "symptom" of an underlying problem—in short that we just do not understand it very well.

This lack of understanding, rather than being a negative force, might have motivated us to further investigation and involvement with alcoholics. Fortunately, this has recently been the case with a sudden upsurge of medical attention to alcoholism. All too often, however, we have relinquished our caretaking position to nonmedical personnel, both lay and professional. No doubt this fact is partly responsible for the emergence of Alcoholics Anonymous as well as the predominance in the field of alcoholism of clergymen, social workers, psychologists, and interested laymen. Notwithstanding the excellent work done by the majority of these people it seems apparent that the physician is best equipped to understand fully the nature of this psychobiologic process. For not only are its etiologic factors a mixture of emotional, social, and biologic forces, but so also are the clinical manifestations and the complications of alcoholism. The same can be said for other drug dependencies.

The "medical model" has been criticized in recent years as an inappropriate way of viewing a number of pathologic conditions. Relevance of this model for mental illnesses, the behavioral disorders, and drug dependencies has been questioned. Critics, too often nonphysicians, mention the traditional concerns of medicine with the structure and function of the body and our resulting avoidance of human experience or the impact of social forces upon the human condition.[1] Further, the medical model, while it focuses on the "disease," ignores the social and ethical significance of behavior—or so some would have us believe. As most physicians know, however, these accusations reveal little understanding of what medicine is all about.

The true "medical model" has, more accurately, something to do with the physician's attention to the patient as an individual, who is the basic unit of care. To understand this person, who has not only biologic but also psychologic and social factors affecting his illness or behavior, is the ultimate goal of the physician. His capacity to weigh the relative importance of these multiple factors is the specific task he faces with each patient. His education equips him to view his patients in a multidimensional setting, the results of this broad assessment constituting the ideal treatment of the whole person.

Certainly the problem of the person who is drug-dependent requires and deserves a multidimensional approach. Alternatives to the more traditional psychosocial therapies, which correctly

*Maslansky, R.: Opiate Addiction 1971. Minnesota Med 54:553, 1971.

emphasize peer-group confrontation and support, plus a "chemical-free" existence, must be scientifically explored. Some of the alternatives now in various stages of experimentation and acceptance include the selective use of disulfiram (Antabuse) as well as antidepressants and tranquilizers for alcoholism, cyclazocine and naloxone (narcotic antagonists) for opiate dependence,[2] and methadone maintenance programs also for narcotic addiction. These approaches, when combined with adjunctive rehabilitative measures, seem to hold considerable promise.[3] They also demand an integration of pharmacology with an understanding of the whole person. This is the medical model. We as physicians must meet the challenge thrust upon us by the drug abuse problem and assume our share of the responsibility for its solution.

Robert M. Morse, M.D.*
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*Mayo Clinic and Mayo Foundation.

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Mild Hypertensive Drugs

I WILL CONSIDER three groups of drugs that I regard as relatively mild in the treatment of hypertension: Rauwolfia compounds, diuretics, and Methyldopa.

Rauwolfia compounds—I still believe that Rauwolfia is one of the most valuable drugs to use in mild hypertension. These drugs are particularly useful in the so-called neurogenic hypertensives, as described by Schroeder. These individuals have tachycardia, appear quite tense, and frequently have a so-called diencephalic flush over the neck and upper chest. Numerous Rauwolfia compounds are available, but I prefer the single pure alkaloid, such as Reserpine. These drugs seem to exert their sympathetic depressant effect centrally and peripherally. They affect the sympathetic discharge from the central vasomotor centers, and they also deplete the terminal postganglionic fibers of their catecholamine stores and thereby inhibit peripheral neurotransmission. This peripheral effect apparently is the more important. In addition, these compounds also have bradycrotic and sedative effects which are particularly useful in individuals with neurogenic hypertension.

The dose-related side effects are more frequently annoying than serious. Nasal stuffiness, increased appetite, fluid retention, nightmares, etc. are all quite common. The more serious side effect is a true psychic depression occurring mainly with high doses. When these drugs were first used in the treatment of hypertension it was not uncommon to prescribe doses of Reserpine as high as 0.25 mg. two and three times a day. The incidence of psychic depression was very high when such doses were used. At the present time I do not use more than 0.1 mg. of Reserpine twice a day. Frequently just 0.1 mg. suffices.

These drugs affect the blood pressure slowly when given orally, and the maximum effect is usually not obtained for three or four weeks. In combination with diuretics these drugs are particularly useful.

Diuretics—Diuretics probably have the greatest over-all use in the treatment of all forms of hypertension, including the milder forms. These drugs have very few side effects, lower both the supine and erect blood pressures, and continue to have effect after prolonged administration.

Initially, these drugs cause a contraction of the extracellular and intravascular spaces and a reduction in cardiac output. These changes last for several weeks but then return to normal even if the drug is continued. The hypotensive effect of these drugs is due to a fall in peripheral vascular resistance seemingly related to a decrease in the water and electrolyte content of the arterial walls. Because of this the various sympathomimetic amines have fewer vasoconstrictive effects.

Although a variety of toxic effects have been reported, they are rare. Agranulocytosis, pancreatitis, intrahepatic cholestasis, nephritis, and

skin rashes have been reported. Probably more important in the day-to-day use of these drugs are the metabolic alterations which can occur. In the presence of renal disease, azotemia may be aggravated. Hyperuricemia also occurs quite frequently, and clinical gout can actually be precipitated. Hyperglycemia also occurs, and blood sugars consistent with mild diabetes mellitus may result. Probably diabetics should not be given these drugs if other drugs are effective. HypoKAlemia occurs in over 50% of patients and should be corrected.

A variety of diuretics are available, all of which seem to have about the same antihypertensive effect. Two newer drugs, Furosemid and Ethacrynic acid have greater diuretic potency but appear to have no greater antihypertensive effects. However, they seem to have a less detrimental effect on renal function and may have a useful role in the presence of severe renal disease.

Methyldopa—It is generally agreed that the amount of tissue catecholamines, especially norepinephrine, is very important in controlling arteriolar tonus, which seems to be a primary defect in hypertension. The synthesis of norepinephrine occurs in the adrenal medulla and also in the granules located in the sympathetic postganglionic nerve terminals. It has been shown that Methyldopa reduces the tissue catecholamine levels in man. The biosynthesis of norepinephrine proceeds from the conversion of dopa to dopamine to norepinephrine. In this reaction, decarboxylation is essential, and compounds like Methyldopa are decarboxylase inhibitors. Although Methyldopa causes a marked decrease in tissue norepinephrine, like Reserpine, this drug does not appear to inhibit the peripheral adrenergic neurotransmission. Methyldopa is converted to alpha-methyl-norepinephrine which displaces the norepinephrine stores. Nerve stimulation proceeds in a normal fashion, but this new chemical acts as a "false transmitter" and does not cause vasoconstriction.

The primary effect of this drug is to reduce peripheral vascular resistance. There is no significant effect on cardiac output, and no significant changes in renal blood flow or glomerular filtration have been observed. Therefore, this drug may have particular usefulness in hypertensive patients with azotemia.

There is a marked variation in dosage requirements. The usual starting dose is about 500 mg. a day, with dosage increase depending on the antihypertensive response. Just as with Reserpine, diuretics potentiate its action.

There are very few serious side effects with Methyldopa. Drowsiness is probably the most common. Occasional febrile reactions and evidence of liver dysfunction have been recorded. It has been reported that a positive Coombs' test without hemolysis occurs in as high as 20 percent of individuals on this drug.

Robert D. Story, M.D.*
Fargo, North Dakota

It's The Law

Physician Not Negligent in Emergency Treatment

After an apparently normal delivery of a healthy child, a woman had a sudden massive vaginal hemorrhage. The attending physician was unable to find the source of the hemorrhage. The patient became unconscious, and her pulse and blood pressure indicated that she was in shock.

An intravenous transfusion into the arm failed. A cut-down was performed in the right ankle. An intravenous drop of fluids and fibrinogen was started. A second cut-down was performed on the left ankle for rapid infusion of blood. One unit of blood was infused in two and one-half minutes, but a second bottle failed to flow properly, and the left leg appeared swollen and cold. The intravenous catheter was immediately removed. The remainder of the blood and drugs was administered through the cut-down in the right ankle. The patient was in deep shock at this time.

With treatment, the patient's condition improved. The left leg continued to be swollen and cold, eventually became gangrenous and required amputation. Examination of the amputated leg revealed necrosis of all tissues from the knee down due to a clot in the popliteal artery.

The patient brought suit against the physician for negligence in connection with the transfusion into her left leg and for causing the loss of that leg. The evidence presented indicated that the patient was in shock for three hours, that the treatment administered was life-saving and major. The jury returned the verdict for the physician.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

You May Be Right

Obscurity

To my way of thinking, some of our medical journals have, during the past years, developed a style of writing designed to impress the reader with the erudition and extensive linguistic ability of the writer. Too often, the result is a style of obscurity which tends to confuse the reader.

The enclosed clipping* ridicules the word "parameter" which has also infested our medical literature.

Recall, if you will, the clear style of Dr. E. T. Bell in his textbook of pathology where each sentence and each word was simple, clear and to the point.

Daniel J. Moos, M.D.
Minneapolis, Minnesota

*Boston Globe

Editor's Note:

You are so right with regard to "parameter's perimeter." I am accumulating a whole series of these words and phrases which I file in my "Bureaucratese Dictionary." I prefer to strike them out from the medical manuscripts, but not infrequently the distressed author avers that he "devoted an hour or two composing" some of those almost meaningless phrases that I heartlessly eliminate in a mere second, almost ruining his manuscript.

Cover Photo

"Nordfjord, Norway"

Dr. Lewis Hanson of Frost, Minnesota, states that the cover photo was taken in June, 1969, with Kodachrome II film. It has particular significance for Dr. Hanson as his mother was born here.

He has been practicing medicine in Frost since November, 1931, and last year, the people of Frost named their new park the "Dr. Lewis Hanson Village Park" after him.

Influenza

It is not merely, as it was long supposed to be, a "pandemic disease" reappearing once or twice in a generation, but it is ever present, now smouldering, and then, every ten, fifteen, or twenty years, bursting into flame.*

*Sir William Hamer, Epidemiology Old and New.

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Physical and Psychological Dependence: Physical and psychological dependence rarely reported. If withdrawal symptoms do occur they may resemble those associated with withdrawal of barbiturates and should be treated in the same fashion. Use caution in administering to individuals known to be addiction-prone or those whose history suggests they may increase the dosage on their own initiative. Repeat prescriptions should be under adequate medical supervision.
Usage in Pregnancy: Weigh potential benefits in pregnancy, during lactation, or in women of childbearing age against possible hazards to mother and child.
PRECAUTIONS: If sleeplessness is pain-related, an analgesic should also be prescribed. Perform periodic blood counts if used repeatedly or over prolonged periods. Total daily intake should not exceed 400 mg, as greater amounts do not significantly increase hypnotic benefits.
ADVERSE REACTIONS: At recommended dosages, there have been rare occurrences of morning drowsiness, dizziness, mild to moderate gastric upset (including diarrhea, esophagitis, nausea and vomiting), headache, paradoxical excitation and skin rash. There have been a very few isolated reports of neutropenia and thrombocytopenia; however, the evidence does not establish that these reactions are related to the drug.

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Editor's Soliloquy

Bureaucratese

BUREAUCRATESE is the jargon of the well-indoctrinated bureaucrat of the lower echelons. It has the synthetic ring of status. If it can be uttered with a scarcely detectable lisp and a slightly halting accent while elegantly caressing the bowl of a tobacco pipe in contemplation of the next phrase, its officiousness becomes assured. No one has the temerity to doubt its authenticity, much less refute it. It becomes gospel. It germinates by arrogating perfectly honorable words from Merriam-Webster dictionary, and then grouping them into confusing phrases connected by articles, prepositions, adjectives, verbs and adverbs. Sentences are also abundantly interspersed with alphabetical conundrums that combine strange three, four, or five capital-letter acronyms meaning something you never heard of, and knowledgeable only within the group that devised them. Figure them out if you can, skip them if you can't; they don't mean much of anything anyway.

Bureaucratese expands into seemingly effortless volumes and conveys almost anything you wish—or nothing at all. It is systematically organized into categories 1, 2, 3 and 4 with sub-categories of a, b, c, d, e and f.

Though it is a universal language for all specialties and sub-specialties, it has its favorite words and phrases within each category.

With the bureaucratic elite of officialdom the verbiage is generously sprinkled with French or Latin idioms designed to disconcert the bourgeoisie, impress the sophisticate and confound the poor secretary who must type it and look up the meaning and spelling on her own time. She wouldn't dare ask the bureaucrat; he couldn't enlighten her, since he himself never knew for sure what the idiom meant. It just sounded good! After the report has been typed it seems so official to the unsuspecting numerical vice-chairman that it passes through him with flying colors, a hearty halloo and a couple of bravos. Only the most naive, conscientious, uninitiated newcomer to the paper-shuffling, hard-chair, small-deck section in the horrendously over-staffed front office would have the unmitigated gall to question either its meaning or its substance.

The author of the inflated report dictated it behind auspiciously closed doors in his elaborately decorated teakwood office, curtained with innerlined floor-to-ceiling drapes over sham windows, while completely relaxed in his high-backed, leather-lined chair, behind his polished uncluttered eight-foot desk with its ornate pen and pencil set. He ordered fourteen Xerox copies to be delivered promptly to the twelve regional directors, where they will be microfilmed and filed for posterity—with two additional copies for his personal memoirs file.

If you wish to acquire the knack, select any two or three words at random; connect them with hyphens, casually add another set, throw in a conjunction, toss in a pronoun; cavarierly interject a comma, colon, semicolon, dash or period to give elan; fondle your pipe, rub your nose, stroke your chin. Try it. Choose your own category. You may be agreeably surprised at your originality and ingenuity, as well as your capacity for gobbledygook.

Fun, wasn't it!

Carl O. Rice, M.D.
Editor-in-Chief

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Review

A-Mode Echoencephalography: A Critical Appraisal

BURTON A. SANDOK, M.D.* and JACK P. WHISNANT, M.D.*

In the past 10 years the use of ultrasound as a diagnostic procedure in neurology has become more common. Although the initial enthusiasm of earlier investigators has been tempered with the passage of time, A-mode echoencephalography has emerged as a useful adjunct in neurologic diagnosis. Experience has shown that, while useful as a screening procedure,[1] the value of echoencephalography is severely limited by several factors, both absolute and relative. A sound understanding of these limitations is essential to the intelligent application of the test.

The purpose of this paper is to emphasize these limitations and to appraise the usefulness of A-mode echoencephalography as a screening procedure.

Absolute Limitations

The absolute limitations are those imposed by the physical principles of ultrasound and cannot, at our present state of technology, be easily overcome.

The frequencies of sound utilized are in the range of one to two million cycles/sec. At these frequencies, sound shows many of the characteristics of light in that it can be refracted or reflected at interfaces of differing acoustic impedances. Because the cerebrospinal fluid and the brain have markedly different acoustic impedances, theoretically one could identify these interfaces and, by relating them to known bony landmarks, map out the size and form of the entire ventricular system.[2] Additionally, one might identify the position of any intracranial tissue, providing it had an acoustic impedance significantly different from that of its neighboring tissue. This opens the possibility for the precise identification and localization of specific intracranial lesions.

Skull Thickness

The opportunities for application of these principles would thus appear to be many and diverse; but their practical application has been shown to be severely limited by several factors. The thickness of the normal skull varies and, because there is a marked attenuation of the sound beam as it passes through the bony skull, in some patients with unusually thick skulls this factor alone can render the examination unsatisfactory.

Area Limits

In order to elicit recordable echoes, the sound beam must intersect the surface under study perpendicularly or nearly so. Thus, in the routine performance of the examination, one is effectively limited to that portion of the brain located between the relatively flat squamous portions of the temporal bones and therefore to an area which transects the third ventricle. Indeed, it has been shown that this is the source of the midline echo complex[3] (Figure 1).

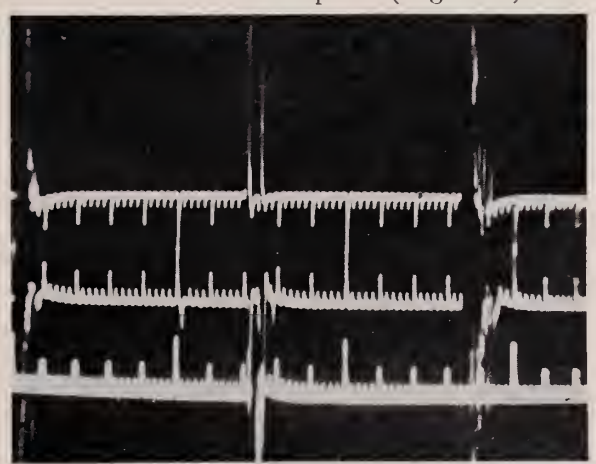


Fig. 1—Normal echoencephalogram. Top trace is right-to-left transmission, middle trace is left-to-right, and bottom trace is through-transmission, revealing theoretic midline.

*Mayo Clinic and Mayo Foundation: Section of Neurology.

Read at the joint meeting of the Minnesota Society of Neurological Sciences and the Mexican Society of Neurology and Psychiatry, Rochester, Minnesota, June 6, 1969.

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Multiple Echoes

In laboratory examination of brain tissue slices, one can identify and localize a large number of at times seemingly strong echoes present on either side of the midline complex.[4] However, in the usual clinical examination, these less well-defined echoes, although noted, remain unidentified, leaving only the strong midline echoes for diagnostic consideration (Figure 2).

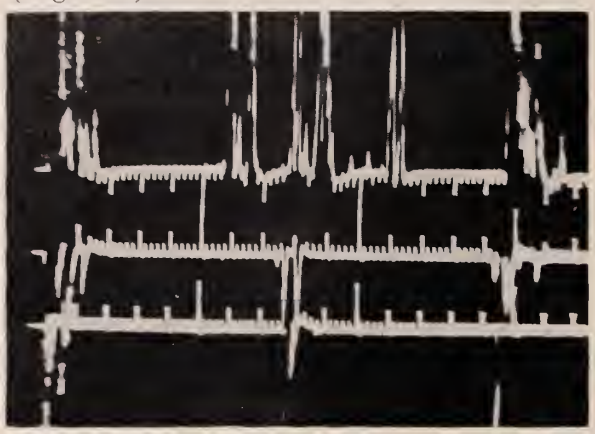


Fig. 2—Illustration of large number of echoes easily obtainable in one normal subject; midline echoes are depicted in lower two traces.

Finally, although there are many documented reports[5-7] of abnormal echoes arising from diseased tissue, often the difference in acoustic impedances between normal and diseased brain tissues is negligible[8] and no abnormal echoes are produced. In those instances in which abnormal echoes are obtained, it is difficult to identify them as being sufficiently distinct from the normally occurring lateral echoes to be of definite diagnostic value (Figure 3).

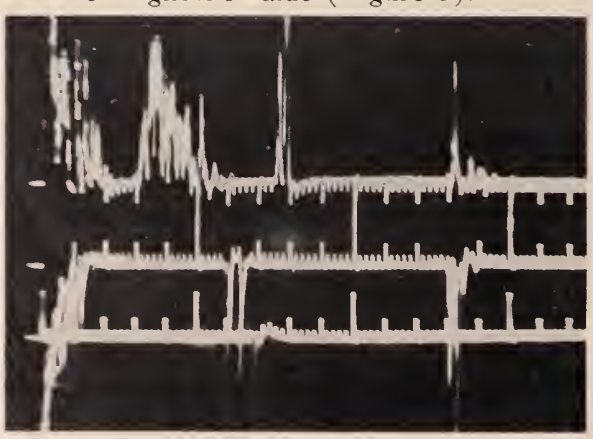


Fig. 3—Top trace shows group of echoes to right of midline, which suggests "tumor echoes." Echo shows 8-mm shift from right to left. Patient was subsequently shown to have metastatic lesion in right temporoparietal region.

Two Diagnostic Parameters

In view of these very definite limitations, the examination as it is usually performed has in fact only two major parameters upon which one can formulate a diagnostic impression. These are (1) the detection of midline position or shift (Figure 4 *left*) and (2) the determination of the size of the third ventricle (Figure 4 *right*).

Relative Limitations

The relative limitations of the test are those imposed by the technique utilized, the pathologic anatomy of the tissue under study, and the experience of the examiner.

Criteria Reducing Subjectivity

The problem of subjectivity and observer bias is admittedly great;[9] however, by demanding strict criteria of verifiability this problem can be eliminated in great part.[10] We have required that the examiner obtain at least two identical sets of pictures which clearly show two symmetric midline echoes. This eliminates the possibility of reporting a spurious midline shift in situations, especially with enlarged ventricles, in which echoes from only one wall of the third ventricle are obtained in the examination (Figure 5). Furthermore, although clear delineation of all near-side and far-side echoes is desirable,[11] we have insisted that, as a minimum, the photographs clearly show accurate alignment (within 2 mm) of at least the far inner tables as well as identical midline complexes in each trace.

Grossman[3] suggested that the third ventricle varies in size and that one can elicit at least four distinct midline echoes. It has been our observation, from comparisons of echoencephalograms and pneumoencephalograms, that this is indeed true and that the third ventricle may present several pairs of potentially parallel surfaces of varying widths, capable of producing a symmetric, double midline complex (Figure 6). Therefore one must realize that of the two measurements mentioned above, that of third ventricular size will be less accurate.

Importance of Midline Shift

Lesions which do not displace midline struc-



Fig. 4—*Left,* Midline shift (3 mm) from left to right in patient subsequently shown to have left parietal meningioma. *Right,* Dilated third ventricle (12 mm) in patient subsequently shown to have cerebellar astrocytoma.

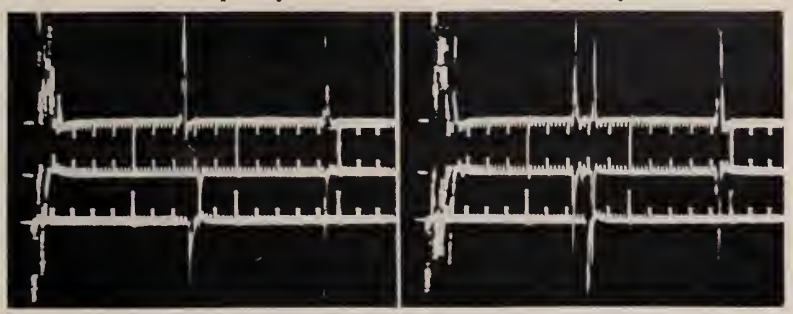


Fig. 5—*Left,* Echoencephalogram shows what appears to be midline shift of 4 mm from left to right. *Right,* When both midline echoes were obtained, correct interpretation—no midline shift, third ventricle 8 mm—is revealed.

tures will not be detected by this test; bilateral lesions or unilateral masses which are frontal, parasagittal, or occipital in location frequently do not cause a shift of midline structures.[8] Obviously a mass in one of these locations can be present even with a normal echoencephalogram. Therefore a normal study should not be used as evidence that a mass does not exist.

At times, in cases of significant midline shift, distortion, or dilatation, truly parallel surfaces may not be present for the perpendicular reflection of echoes, and reliable echoes cannot then be obtained. One must therefore appreciate that technically difficult studies, although associated with a high percentage of abnormalities,[12] are likely to be less accurate than those studies in which the echoes are easily and reproducibly obtained.

Possibility of Error

Neither the echoencephalogram nor the examiner is infallible. We have encountered rare instances in which apparently verifiable midline shifts were demonstrated and later shown to be in error. We have seen, also rarely, a seemingly normal echo in the presence of what was shown to be a significant midline shift at later angiography. At times we have noted instances of apparent midline abnormalities "corrected" or "produced" when the test was repeated by another, usually unbiased and perhaps more experienced, examiner not involved in the direct clinical care of the patient.

It is clear that accuracy is intimately related to the experience of the examiner.[13]

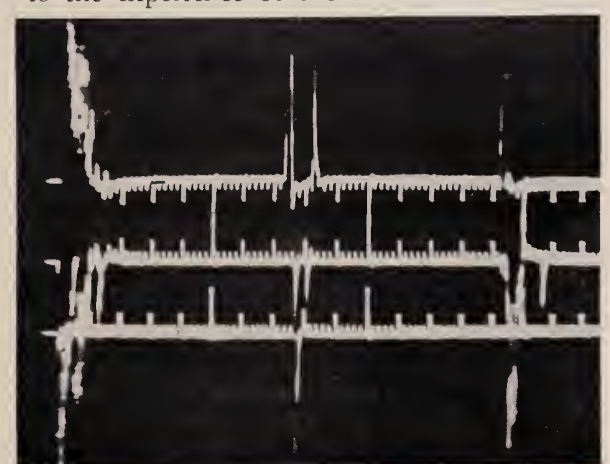


Fig. 6—Top trace, showing midline width of 8 mm, and middle trace, showing midline width of 4 mm, were easily obtainable from normal control subject whose theoretic midline is indicated on bottom trace.

Clinical Application

Although echoencephalography does not provide the clinician with a diagnosis, it can assist him in making certain inferences as to the nature and location of the lesion under consideration. For example, one can utilize information regarding the direction and degree of shift, combined with the clinical evaluation and electroencephalogram, to indicate whether the responsible pathologic lesion is of an expanding nature (the shift being away from the site of presumed abnormality) or of an atrophic nature (the shift being toward the involved side).[14] Such a differentiation, in certain cases of focal convulsive disorders,[15] cannot easily be made on other grounds, short of a contrast study.

Additionally, measurement of third ventricular size affords further diagnostic help. Enlargement implies the presence of hydrocephalus. However, on echoencephalographic grounds alone one cannot distinguish reliably between hydrocephalus ex vacuo (as seen with degenerative disorders) and hydrocephalus associated with increased intraventricular pressure.

Conclusion

A-mode echoencephalography, although approaching an accuracy of greater than 90%,[10,16,17] is not a substitute for any existing neurodiagnostic procedure. There are a wide variety of clinical situations in which this test has been proved to be valuable,[18] generally in those instances in which an estimate of the position of the midline structures and the size of the third ventricle might be of value in the differential diagnosis.

The use of A-mode echoencephalography as a screening procedure has certain limitations. Understanding these limitations greatly increases the value of the procedure.

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12-18. May be secured from the author or the reprints.

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*Modern Handbook of Humor, Ralph Woods, Editor.

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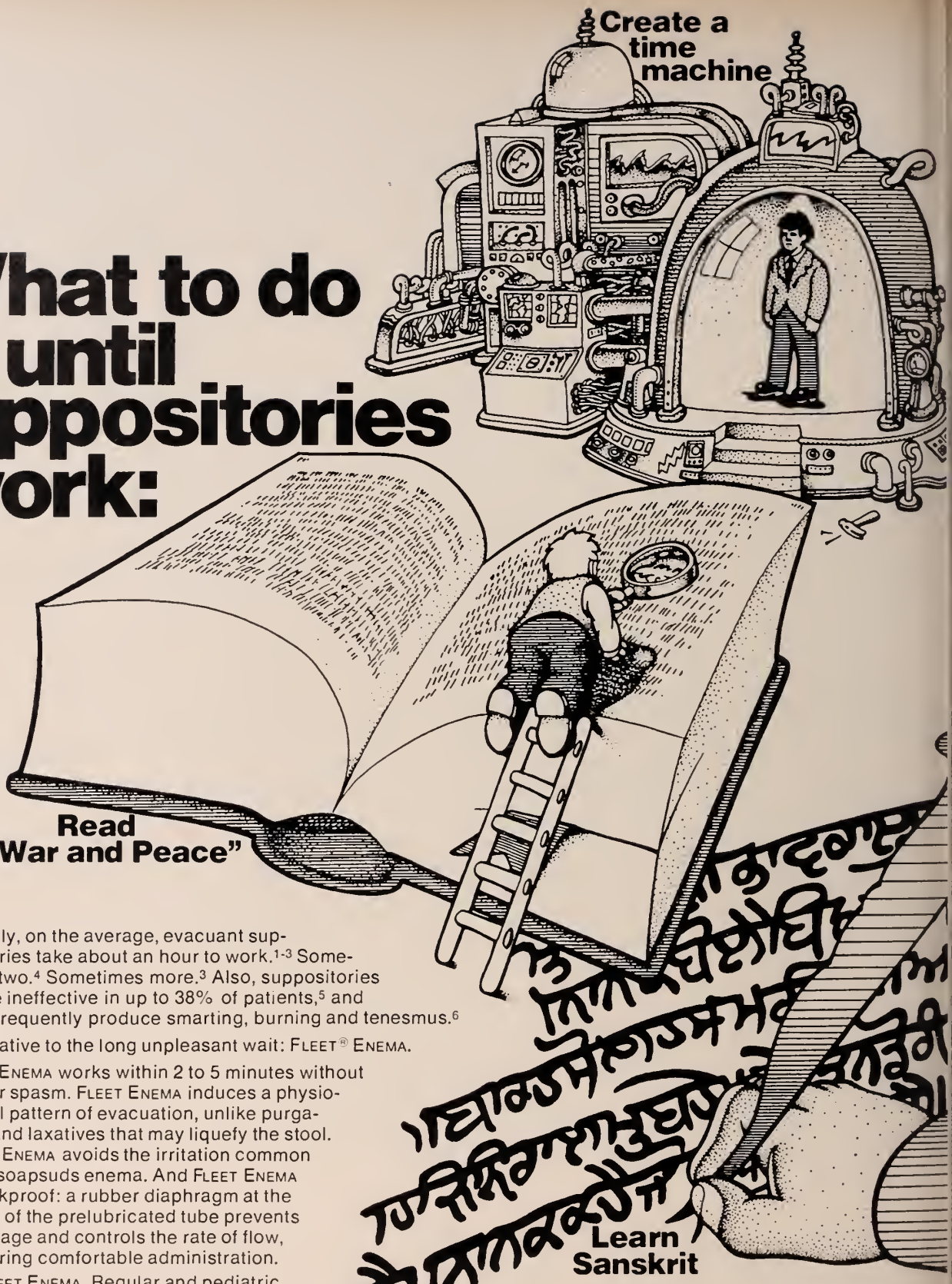
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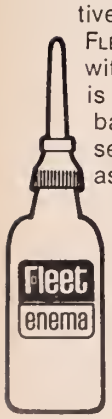
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Warning: Frequent or prolonged use of enemas may result in dependence. Take only when needed or when prescribed by a physician. Do not use when nausea, vomiting or abdominal pain is present.
Caution: Do not administer to children under two years of age unless directed by a physician.

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Tumor Conference

Fibrosarcoma of the Mandible

PETER R. JOCHIMSEN, M.D.* and THEODOR B. GRAGE, M.D.*

THE MANAGEMENT of the patient with fibrosarcoma of the mandible poses a variety of diagnostic and therapeutic problems. Although fibrosarcoma is the most frequent malignant tumor of connective tissue, its occurrence in the mandible is rather uncommon. Reviewing the English medical literature we found only 25 documented cases of mandibular fibrosarcoma. This number is too small to permit firm conclusions regarding the clinical course, the gross and microscopic pathology, the optimum form of treatment, and the prognosis of this unusual neoplasm.

The clinical and pathological features of three patients with fibrosarcoma of the mandible treated at the University of Minnesota Hospitals are presented to characterize certain features of this tumor.

Case Reports

Case 1

Clinical Course

This 33-year-old man was first seen in 1955 with a four-week history of a painful mass in the right lower jaw, for which a dentist had been treating him with injections of penicillin. The patient continued to complain of difficulty in chewing foods, numbness in the right side of the face, and occasional stabbing pain in the area of the mass. A biopsy of the mass disclosed an undifferentiated malignant tumor and the patient was referred to the University

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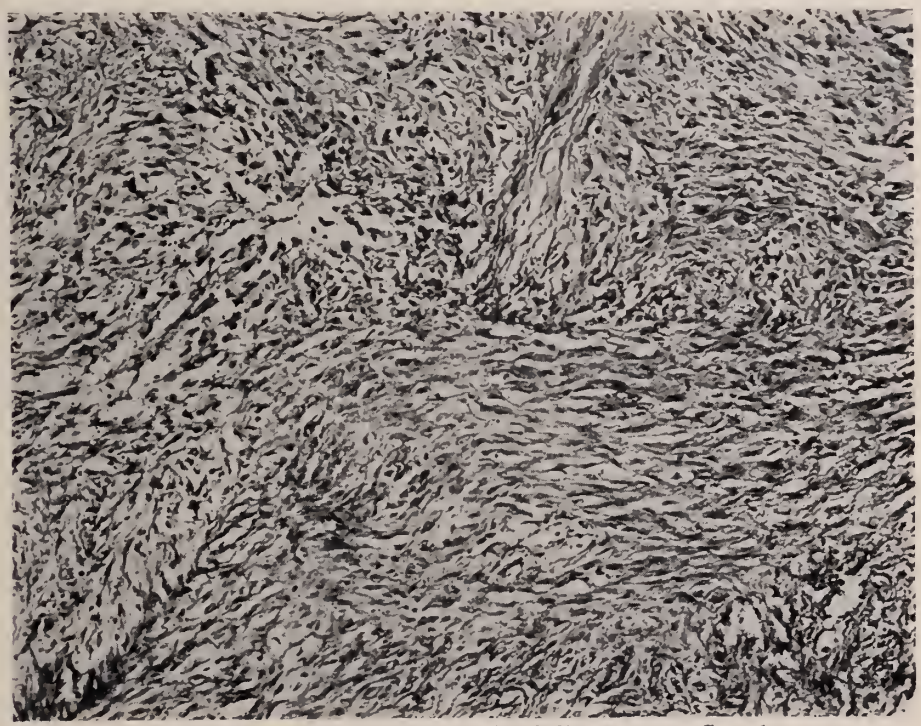


Fig. 1—Moderately well differentiated fibrosarcoma—Case 1.

of Minnesota Hospitals for treatment.

Examination revealed a 5-cm. rounded, tender mass in the right mandibular alveolar ridge, adjacent to the second molar. Radiographically the lesion had produced an osteolytic defect. There was no evidence of metastatic disease. After a preliminary tracheostomy and gastrostomy, a right hemi-mandibulectomy and right radical neck dissection with a left supra-hyoid node dissection was performed. The postoperative recovery was uneventful.

Pathology

The gross tumor measured 5 × 2 ×3 cm. and appeared to arise in the mandible, with extension into the bone. Upon microscopic examination the cells were found to be moderately well differentiated, although mitoses were frequently seen (Figure 1). Bizarre forms of tumor cells were not uncommon. The pathologist classified the tumor as a moderately undifferentiated fibrosarcoma. Examination of numerous lymph nodes removed with the specimen failed to reveal nodal spread of the tumor.

Follow-up

The patient remained clinically free of disease for a period of one year, when a mass was noted in the right pre-auricular area. A wide radical resection of the recurrent tumor was attempted, but due to extension of the tumor into the pterygoid fossa, deep to the zygoma, and into the floor of the right orbit, the lesion was incompletely removed.

External radiation therapy was directed to the area of the residual tumor mass without evidence of regression. The patient died approximately one year later from massive local recurrence.

Case 2

Clinical Course

This 31-year-old man was admitted to University of Minnesota Hospitals in 1956 with a four-month history of a small lesion between the medial and lateral incisor teeth in the right lower jaw. An incisional biopsy, performed at the University of Minnesota Dental School prior to admission, revealed the mass to be a well differentiated fibrosarcoma.

Physical examination, on admission, showed a firm, 1 × 1-cm. mass in the right lower mandible on the buccal surface; roentgenograms of the mandible revealed no bony abnormality. Under local anesthesia a marginal resection of the mandible was performed. All gross tumor was removed with a margin of uninvolved tissue.

Pathology

The resected specimen consisted of a portion of mandible with attached tissue from the alveo-



Fig. 2—Histology of Case 2, demonstrating spindle cell nature of the low-grade fibrosarcoma.

lar ridge. Microscopic examination showed a fibrosarcoma of low-grade malignancy characterized by spindle-shaped cells with small dark-staining nuclei of relatively uniform shape (Figure 2). Few mitotic figures were identified. Some of the nuclei were relatively large. The margins of resection were free of tumor.

Follow-up

The patient has been followed in the University of Minnesota Hospitals Tumor Clinic for a period of six years without evidence of recurrence.

Case 3

Clinical Course

A 17-year-old woman was admitted to University of Minnesota Hospitals on July 25, 1967. She had noted a small mass in the right mandible just below the canine tooth two months prior to admission. The lesion had not increased in size and there was no history of bleeding or ulceration. An incisional biopsy of the mass had been performed prior to admission and histological examination disclosed a well differentiated fibrosarcoma. Prior medical history was unremarkable.

Physical examination revealed a well developed, slightly obese girl. The only significant finding was a 1 × 1-cm. firm protruberant mass on the anterior surface of the mandible, 3 cm. lateral to the midline on the right. Sutures were present from the previous incisional biopsy. Laboratory studies were within normal limits, as were roentgenograms of the mandible.

Under general nasotracheal anesthesia a marginal resection of the mandible was performed. The segment of mandible containing the tumor, with three attached teeth, was removed with a margin of 1 cm. of uninvolved tissue around the lesion in all planes. The patient was discharged on the third postoperative day.

Pathology

The gross specimen consisted of a segment of the right mandible, containing three teeth. On the gingival surface was an 8-mm. raised plaque, 2 mm. thick, approximately midway between the cut surfaces.

Permanent sections of the resected specimen demonstrated bone and dense fibrous tissue lined by benign gingival epithelium. The submucosa was almost entirely replaced by streams and whorls of fibrous tissue cut longitudinally and in cross section (Figure 3). The tumor cells exhibited some variation in nuclear size and shape. Occasional mitoses, approximately one per three high-power fields, were seen. The resected margins were free of tumor. The pathological diagnosis was a low-grade fibrosarcoma of the gingiva of the mandible.

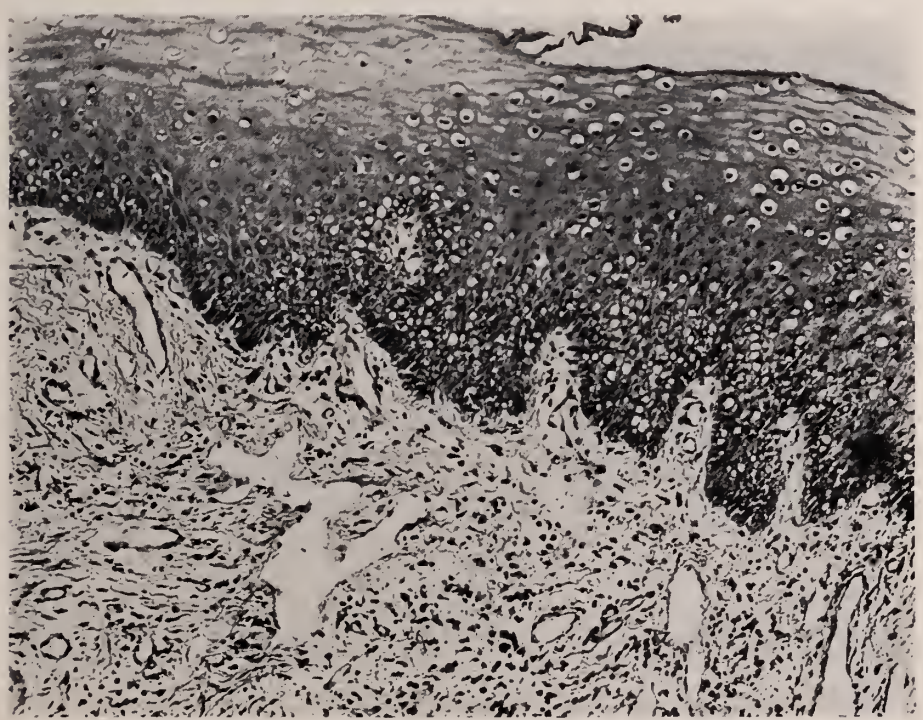


Fig. 3—Low-grade fibrosarcoma adjacent to gingival epithelium —Case 3.

Follow-up

The patient was followed in the Tumor Clinic for two years without evidence of recurrence. She was fitted with a dental prosthesis and the cosmetic result was good.

In November of 1969 the fibrosarcoma recurred on the lingular aspect of the right mandible, extending somewhat posteriorly, measuring 2 × 4 × 2 cm. with obvious invasion of the mandible itself. There was no evidence of nodal involvement in the neck. Physical examination and laboratory evaluation were within normal limits. A panorex view of the mandible revealed an osteolytic defect in the mandible, adjacent to the area of the previous marginal resection (Figure 4).



Fig. 4—Osteolytic recurrence of low-grade fibrosarcoma seen in mandible —Case 3.

Under general anesthesia a right hemi-mandibulectomy was performed including a radical resection of the structures of the floor of the mouth in order to widely circumscribe the recurrent lesion. For cosmetic reasons the mandibular arch was reconstructed, using a portion of the 8th rib, which was slotted into the symphysis and into the posterior ramus of the mandible and secured with a Kirschner wire.

The immediate postoperative recovery was uneventful. The cosmetic result was acceptable, as was the functional result in terms of speech and mastication.

Histological examination of the removed specimen revealed a well differentiated fibrosarcoma, identical in appearance to the original tumor.

Two months later the grafted rib had to be removed because of infection. The patient is presently being fitted with an orthodontic prosthesis to minimize lateral displacement of the residual mandible and the resultant malocclusion and to provide her with a cosmetically more acceptable situation. The patient has now been followed for four years since her initial operation, and she appears to be free of tumor.

Review of the Literature

In Stout's series of 218 cases of fibrosarcoma, only three occurred in the mandible.[1] A somewhat higher incidence was reported by Dahlin and Ivins of the Mayo Clinic, who described 13 fibrosarcomas of the mandible in 114 cases of fibrosarcoma of bone.[2] We were able to cull an additional nine cases from the literature, usually reported in the form of isolated case reports.[3-10]

Clinical Features

Although fibrosarcomas are most frequently seen in the third through fifth decades of life, no age group is exempt. The majority appear to occur in males. Patients with fibrosarcoma of the mandible commonly describe the presence of a slowly growing, palpable, non-tender mass in the gingiva of the lower jaw. Occasionally invasion of the mandible has occurred and the patient complains of pain or numbness, indicative of neural involvement. De-

formity of the jaw, with difficulties in mastication, or a pathological fracture of the mandible are seen late. In certain instances the disease is first suspected when the patient seeks help from the dentist because of a loose tooth, or because of a suspected periodontal infectious process.

Classifications of Malignant Tumors of Mandible

Pekarsky has classified the sarcomas of the oral cavity according to histologic types as follows.[11]

Fibrosarcoma	Malignant vascular tumors
Rhabdomyosarcoma	Ewing's tumor
Leiomyosarcoma	Malignant melanoma
Lymphosarcoma and reticulum cell sarcoma	Osteogenic sarcoma
	Chondrosarcoma

These sarcomas, along with carcinomas and metastatic tumors to this area, make an impressive list of possible malignancies causing masses in the mandibular area.

In general, benign tumors of the mandible and the gingiva are far more common and include such lesions as hemangioma, neurofibroma, myoma and myxoma. Only by microscopic examination of the tumor can its true nature be identified.

Histopathology

Fibrosarcomas of the mandible arise from the periosteum or the connective tissue surrounding the mandible. Although a central or endosteal fibrosarcoma of the mandible has been described, its existence has been questioned by Stout and Geschickter.[1,13]

Most fibrosarcomas of the mandible appear to be well-differentiated with little tendency to metastasize, though local recurrence is common (see Cases 1 and 3). Occasionally, more undifferentiated fibrosarcomas of the mandible have been described which exhibit a more aggressive growth pattern and ultimately result in the death of the patient from uncontrolled local recurrence, distant metastases, or both.

Histologic evaluation of the spindle cell lesion is extremely difficult. As MacKenzie points out, "The histopathologist has to decide in any given case whether the lesion is truly fibroblastic in type, and if so, where it lies among the wide, gradually varying spectrum of fibroblastic proliferations."[12]

Stout has indicated that the diagnosis and grading of a fibrosarcoma may not always be made on the basis of histology alone, and that clinical behavior may in certain cases suggest the nature of some lesions.

That histologic diagnosis is difficult, if not impossible at times, is borne out by a report of Conley dealing with an analysis of 84 patients with an original diagnosis of fibrosarcoma of the head and neck.[16] Dr. Stout reappraised all the cases in this series and, of 54 determinate cases, identified 23 percent as undifferentiated fibrosarcoma and 77 percent as fibromatosis or differentiated fibrosarcoma. The term "fibromatosis" is not a good choice and we prefer to classify these lesions as well differentiated fibrosarcomas. In the group of patients with "fibromatosis" (differentiated fibrosarcoma) 79 percent were apparently cured, while 21 percent were either dead from their neoplasm or living with disease; all of those who succumbed died from persistent local disease, except for one patient who had distant metastasis . . .[16]

Such a clinical course is not compatible with a benign connective tissue proliferation, as the term "fibromatosis" implies.

Treatment

Surgical resection offers the only chance for control of fibrosarcoma of the mandible. Treatment is primarily directed at permanent eradication of the disease. Preservation of function and cosmesis is a major, though secondary objective.

In the anaplastic or undifferentiated tumors, or in those tumors in which invasion of the mandible has occurred, a wide resection is required, as exemplified by Case 1. In other instances a marginal resection of the mandible may be feasible, if the lesion is well-differentiated and small (Case 2). Because of the infiltrative tendency of the tumor a wide margin of healthy normal tissue must be excised. Defects thus created may often be adequately managed through the use of prosthetic devices. The tendency for local recurrence of the well differentiated fibrosarcoma, despite a seemingly adequate resection, is well demonstrated in Case 3.

Fibrosarcomas rarely metastasize to the regional lymph nodes; a radical neck dissection in fibrosarcoma of the mandible should be reserved for those patients who have clinically palpable nodal involvement.

In general, fibrosarcomas are not radiosensitive tumors; however, radiation therapy has been used in some instances for palliation. Chemotherapy has been employed infrequently and does not appear to be of value.

Prognosis

The five-year survival rate of 59 percent of the patients with fibrosarcomas of all sites, as reported by Hare and Cerny, is almost identical to the five-year survival rate reported by Pack and Ariel.[14,15] It appears that fibrosarcomas of the mandible have a somewhat more favorable outlook than the above figures would indicate. As already pointed out, the fibrosarcomas of the head and neck are found to be preponderantly of the differentiated or low-grade type, with a high resectability rate and infrequent distant metastases.

The local recurrence rate for both the high-grade and the low-grade lesion is high in most of the reported cases. In the Hare and Cerny series, the recurrence rate of all fibrosarcomas was 60.4 percent, and in the Pack and Ariel series, 56 percent.

Conclusions

The prognosis following surgical excision of a fibrosarcoma of the mandible appears to be good. Patients with localized disease and well differentiated tumors treated by wide surgical excision appear to have the best prognosis.

Because of the high incidence of local recurrence it is essential that a patient who has been treated for a fibrosarcoma be followed at regular intervals for many years. A local recurrence, particularly of the low-grade fibrosarcomas, does not indicate a hopeless prognosis and may well lend itself to a radical resection with a good chance for ultimate control of the neoplasm.

References may be secured from the author or the reprints.

The hand that lifts the cup that "cheers," should not be used to shift the gears.

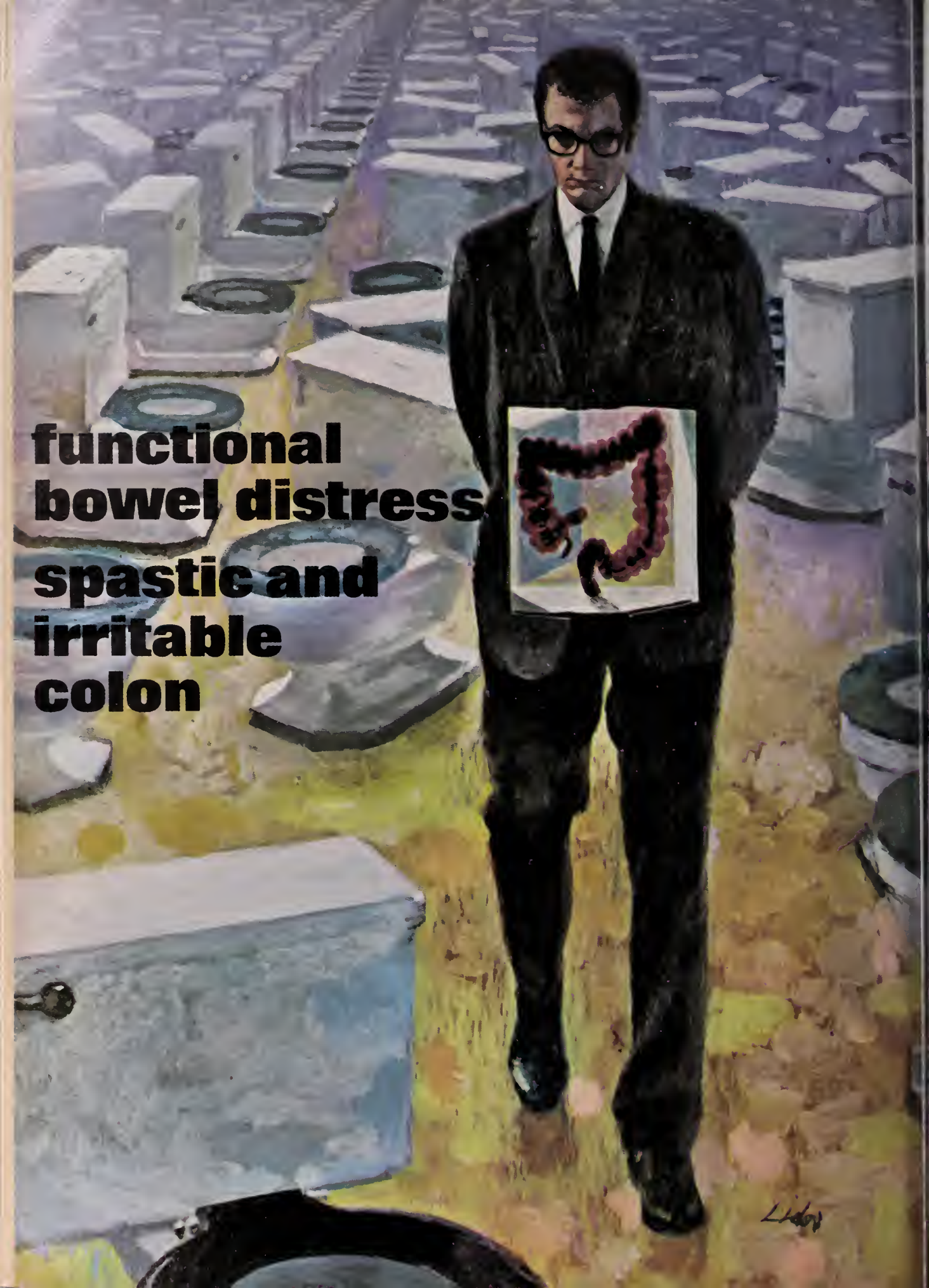


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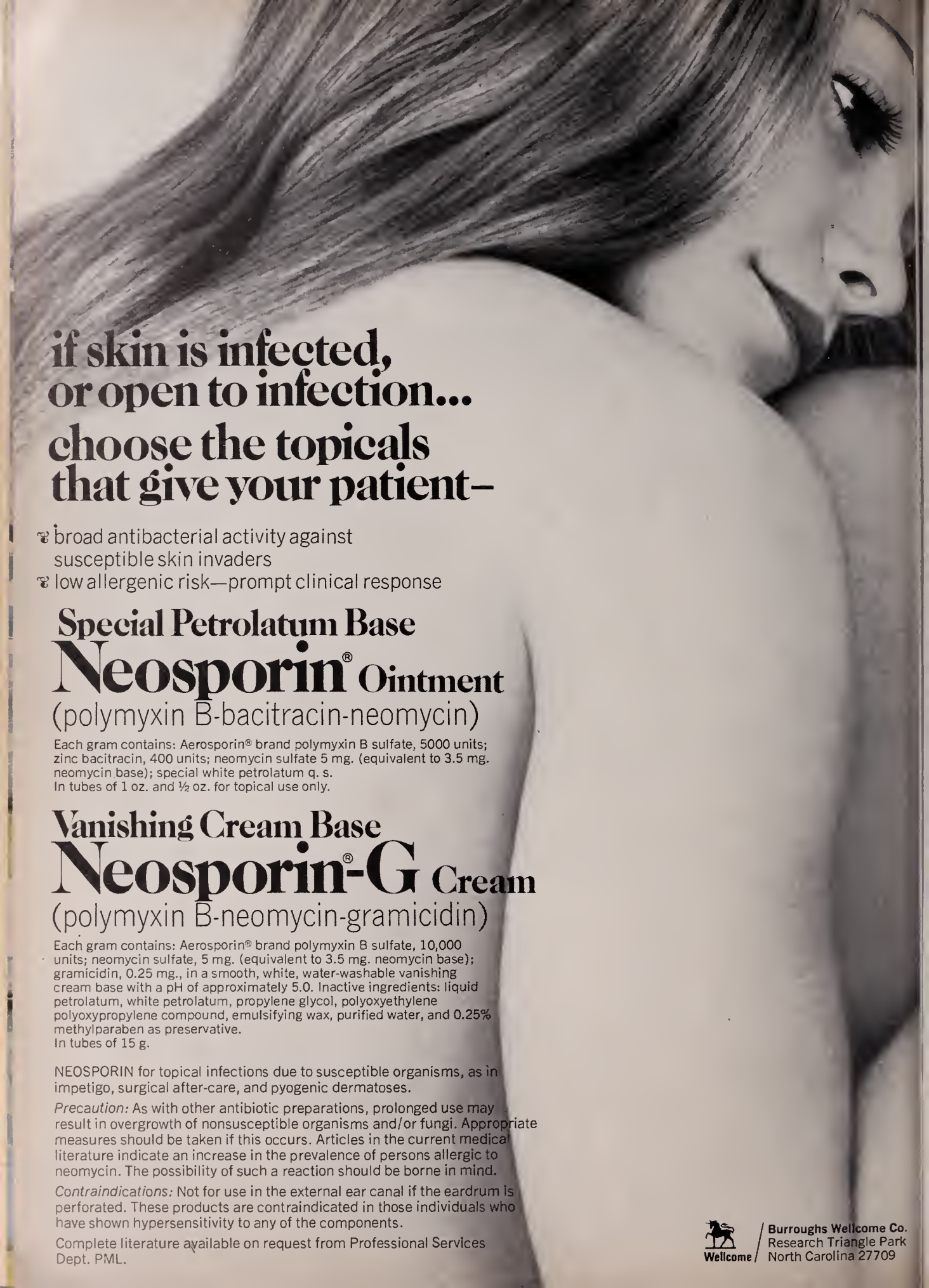
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■ **INDICATIONS** Robinul Forte (glycopyrrolate, 2 mg.) and Robinul-PH Forte are double-strength dosage forms of glycopyrrolate. They are primarily indicated for patients who are less responsive to anticholinergic therapy and for control of the more prominent symptomatology associated with acute episodes of gastrointestinal disorders. Emphasis should be on total management, with due consideration of the various therapeutic modalities available, including diet, antacids, anticholinergic agents, sedatives, and attention to emotional problems. Accordingly, glycopyrrolate is recommended in the management of gastrointestinal disorders amenable to anticholinergic therapy, such as: (1) duodenal ulcer, duodenitis, pylorospasm; (2) gastric ulcer, gastritis, esophageal hiatal hernia, hyperchlorhydria, pyrosis, aerophagia, gastroenteritis; (3) esophagitis; (4) cholecystitis, chronic pancreatitis; (5) spastic and irritable colon, ulcerative colitis, functional bowel distress, diverticulitis, acute enteritis, diarrhea; and (6) splenic flexure syndrome, neurogenic gastrointestinal disturbances. When these conditions are associated with psychic overlay, the formulation with phenobarbital may be indicated. ■ **CONTRAINDICATIONS** Glaucoma, urinary bladder neck obstruction, pyloric obstruction, stenosis with significant gastric retention, prostatic hypertrophy, duodenal obstruction, cardiospasm (megaesophagus), and achalasia of the esophagus, and in the case of Robinul-PH Forte (glycopyrrolate with phenobarbital), sensitivity to phenobarbital. ■ **PRECAUTIONS** Administer with caution in the presence of incipient glaucoma. ■ **SIDE EFFECTS** The most frequent side effect noted during clinical trials was dry mouth. Thirty-three (3.3%) of 1,009 patients receiving 1 to 32 mg. of glycopyrrolate a day complained of dry mouth of moderate to severe degree, but only 11 discontinued treatment because of this. Blurred vision, constipation, and urinary hesitancy have been reported infrequently. Other side effects associated with the use of anticholinergic drugs include: tachycardia, palpitation, dilatation of the pupil, increased ocular tension, weakness, nausea, vomiting, headache, dizziness, drowsiness, and rash. ■ **DOSAGE** The average and maximum recommended dose of Robinul Forte (glycopyrrolate, 2 mg.) or Robinul-PH Forte is one tablet three times daily (in the morning, early afternoon, and at bedtime). To obtain optimum results, dosage should be adjusted to the individual patient's response. After the more severe symptoms associated with acute conditions have subsided, the dose may be reduced to the minimum required to maintain symptomatic relief. ■ **SUPPLY** Robinul Forte (glycopyrrolate, 2 mg.) is available as scored, compressed pink tablets engraved AHR/2 in bottles of 100 and 500. ■ Robinul-PH Forte (glycopyrrolate, 2 mg., with phenobarbital, 16.2 mg.) is available as scored, compressed blue tablets engraved AHR/2 in bottles of 100 and 500.

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Case Report

Profound Diuresis Associated with Mitral Regurgitation

A Case Report

THOMAS V. MEARS, M.D.,* ALEXANDER A. LEVITAN, M.D.,† MICHAEL J. RIETBROCK, M.D.,§ HARLEN HAWKINSON, M.D.‡ and GERALD B. LEE, M.D.#

A 53-year-old white female presented at St. Paul-Ramsey Hospital with a four-week history of increasing shortness of breath, abdominal distention and colossal edema. She had had chorea during childhood. She had been overweight almost her entire life, and under medical management numerous attempts at weight reduction had been only transiently successful. Three years before she had been hospitalized because of the onset of atrial fibrillation and was started on digitalis. Since that time she had noted dyspnea on exertion and intermittent paroxysmal nocturnal dyspnea. Subsequently, various diuretic regimens and thyroid extract had been employed in an attempt to reduce her ever-increasing size. Two months before this admission to our hospital she had noted the onset of hoarseness.

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Physical examination showed her blood pressure to be 110/70 mm Hg; pulse 60/min. and irregular; respiratory rate, 30/min. She weighed 354½ pounds. Wasting of the facial musculature and arms was noted. The external jugular veins filled to 45°; prominent CV waves were visible. The lungs were clear to percussion and auscultation. Examination of the heart showed the point of maximum to be in the fifth intercostal space at the anterior axillary line. A systolic thrill was palpable at the apex and there was a sternal heave. A grade iv/vi holosystolic high frequency murmur was heard at the apex and radiated to the left axilla. A high frequency grade ii/vi systolic murmur, which became accentuated during inspiration and was heard best in the region of the xiphoid, was also noted. S_2 was split physiologically but P_2 was louder than A_2. The abdomen was markedly distended with ascites; she had 4+ pitting edema to the thorax. Indirect laryngoscopy revealed paresis of the left vocal cord.

Laboratory data revealed a hemoglobin of 11 gm %. Urinalysis showed 1+ albuminuria. The BUN was 35

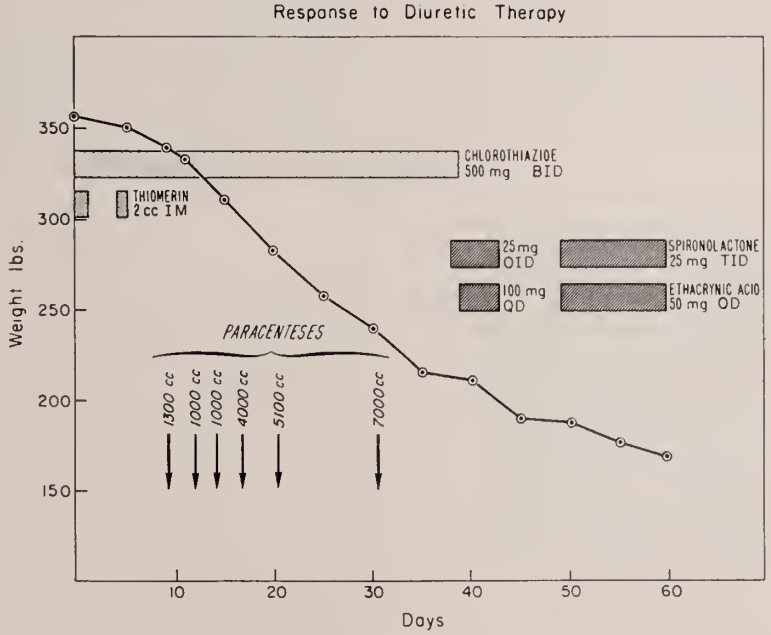


Fig. 1—Note that paracenteses were performed six times.

mgm %, uric acid 11.3 mgm %, total serum bilirubin 1.4 mgm % and the BSP 25.5 % retention. The WBC, total serum protein and A/G ratio, serum calcium and phosphorus, alkaline phosphatase, PBI, SGOT, and serum electrolytes were normal. Admission electrocardiogram showed atrial fibrillation with a slow ventricular response and ventricular bigeminy. ST-T wave changes suggested left ventricular strain. The chest x-ray showed generalized cardiomegaly plus moderate pulmonary vascular congestion. Cardiac fluoroscopy revealed biventricular and left atrial enlargement.

The patient's hospital course was one of progressive improvement. Orthopnea required chair rest for the first three weeks. Initially she was treated with thiomerin and chlorthiazide diuretics (Figure 1). A total of 19.4 L was removed by abdominal paracentesis for symptomatic relief. The total weight loss sustained by the patient through diuresis and paracentesis was 191 pounds during the 61-day period of hospitalization. During this time her serum electrolytes and serum proteins remained normal. Digitalis had been withheld on admission because of the bigeminal rhythm. She was redigitalized and discharged on digitoxin, chlorothiazide, spironolactone, and KCl.

In the ensuing two-month interval the patient remained asymptomatic but had reaccumulated 23 pounds of edema fluid. She was readmitted to the hospital for revaluation. Following a 20-pound diuresis she underwent right and left heart catheterization.

Cardiovascular Pressures	Phasic Pressure	Mean Pressure	Exercise
Right Atrium	5/2	4	7.5
Right Ventricle	31/4	—	40/7
Pulmonary Artery	25/12	19	27
Distal Pulmonary Artery	13/6	10	—
Left Ventricle	114/8	—	—
Aorta	110/72	85	—

Cardiac Output = 4.6 L/min (at rest)
Cardiac Index = 2.4 L/M²/min.

The ventriculogram showed 4+ mitral insufficiency and moderate left atrial enlargement (Figure 2). A liver biopsy was performed and revealed mild portal fibrosis. She was discharged but, despite close medical followup, she again accumulated fluid, and surgery was recommended.

A #3 Starr Edwards mitral prosthesis was inserted. The tricuspid valve appeared normal although there was dilatation of the valve annulus. Since surgery she has done well but has required 500 mg chlorthorazide daily to prevent fluid retention. In reviewing the literature, we believe that this patient represents a record for diuresis occurring with mitral insufficiency due to rheumatic heart disease.

Discussion

This patient presented with severe edema which was related to her relative tricuspid insufficiency. In the presence of mitral valvular disease clinically and hemodynamically, significant tricuspid insufficiency is not an infrequent occurrence. Braunwald et al.[1] reviewed 100 patients who had undergone mitral valvulotomy and 28 of these were noted to have tricuspid insufficiency. Twenty-one of the 28 had primary mitral insufficiency. The regurgitation is probably due to the right ventricular hypertension and subsequent dilatation of the tricuspid annulus. At surgery the tricuspid valve is usually anatomically normal. It must be assumed in our patient that her improving clinical course and diuresis on the initial hospitalization were due to the improvement in the degree of tricuspid insufficiency mediated through diuretics and prolonged chair and bed rest. About a third of the patients with tricuspid insufficiency have severe edema.[2]

This patient also presented with hoarseness, probably due to left recurrent laryngeal nerve paresis. Ortner in 1897 first reported the as-

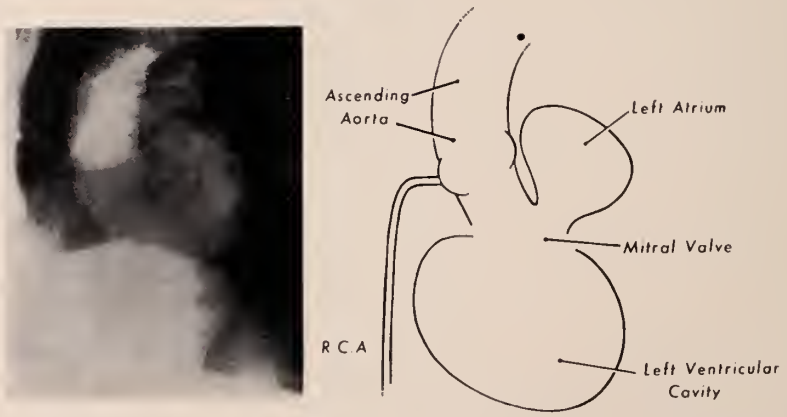


Fig. 2—There were no premature ventricular contractions during the left ventriculogram.

sociation in two cases of hoarseness with mitral stenosis, which has been subsequently called Ortner's syndrome. In heart disease it is a rare occurrence but still remains associated primarily with mitral stenosis.[4] Camishion et al.[5] reviewed 142 patients with mitral valvular disease with left recurrent laryngeal nerve paralysis; 103 had mitral stenosis. In only three adults did they find isolated mitral insufficiency. The paralysis is thought to be due to the compression of the nerve between the enlarged left pulmonary artery and the aorta at the ligamentum arteriosum. There has recently been a report of a 14-year-old girl with mitral regurgitation whose presenting symptom was hoarseness.[7]

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School of Salernum IV

The *Melancholly* from the rest do varie,
Both sport and ease, and company refusing,
Exceeding studious, ever solitary,
Inclining pensive still to be, and musing,
A secret hate to others apt to carry:
Most constant in his choise, tho long a chusing,
Extreme in love sometime, yet seldom lustfull,
Suspitious in his nature, and mistrustfull,
A wary wit, a hand much given to sparing,
A heavy looke, a spirit little daring.

At the opposite pole from the sanguine extrovert the School places the melancholy introvert. Conservative, studious, circumspect, withdrawn, he is slow and reluctant to commit himself, but once committed he is constant. Like the flegmatic, however, he will never set the world on fire.

Verbosity?

Many a tourist to my native Brown County, Indiana, has been completely astonished at the literacy and lucidity of one of the highly educated old-timers there. Not infrequently, touring city dwellers have commented to him as he sat in his porch swing sucking on his corn-cob pipe, "Doesn't it get pretty lonesome around here?"

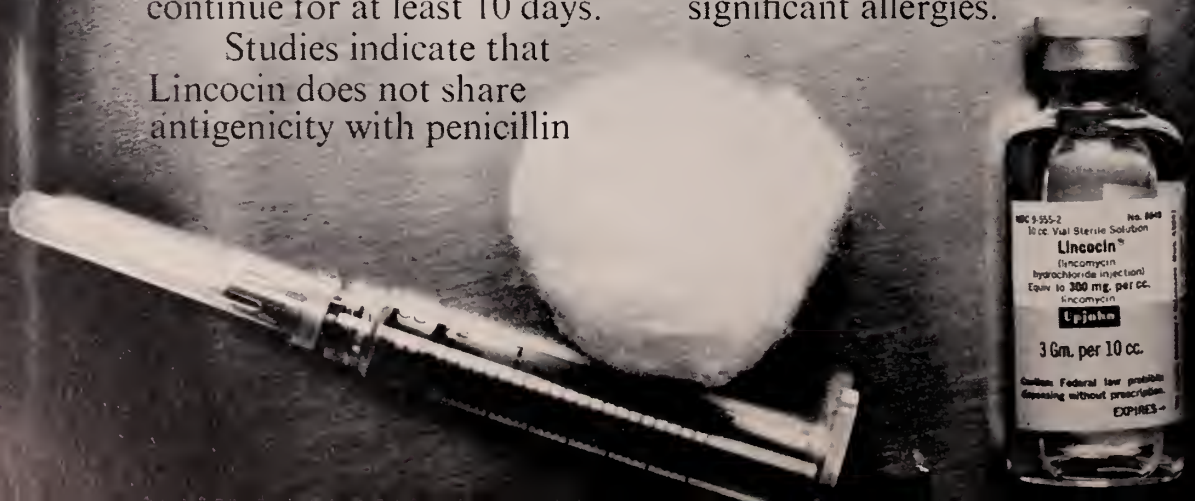
Preceded first by a well-aimed spit and then a shift of his corn-cob pipe he delivers his surprising philosophical reply, "Solitude exists only as a temporary function of the mind's reaction to one's surroundings, inoculating those affected with considerable success. Being indigenous to this primeval forest and having suffered from claustrophobia in my youth, I find habitation in nature's scenic wonderland not only tranquil and satisfying, but essentially compulsory."*

*M. Dale Baughman.

Hypersensitivity to penicillin is a good reason to consider Lincocin®
(lincomycin hydrochloride)

Lincocin (lincomycin hydrochloride, Upjohn) has produced a high percentage of satisfactory responses in patients with mild, moderate and severe infections due to susceptible streptococci, pneumococci and staphylococci (including many penicillinase-producing strains). With ß-hemolytic streptococcal infections, treatment should continue for at least 10 days.

Studies indicate that Lincocin does not share antigenicity with penicillin compounds. However, hypersensitivity reactions such as angioneurotic edema, serum sickness and anaphylaxis have been reported, some of these in patients known to be sensitive to penicillin. As with any antibiotic, Lincocin (lincomycin hydrochloride, Upjohn) should be used cautiously in patients with histories of asthma or other significant allergies.



So is penicillin-resistant staph.

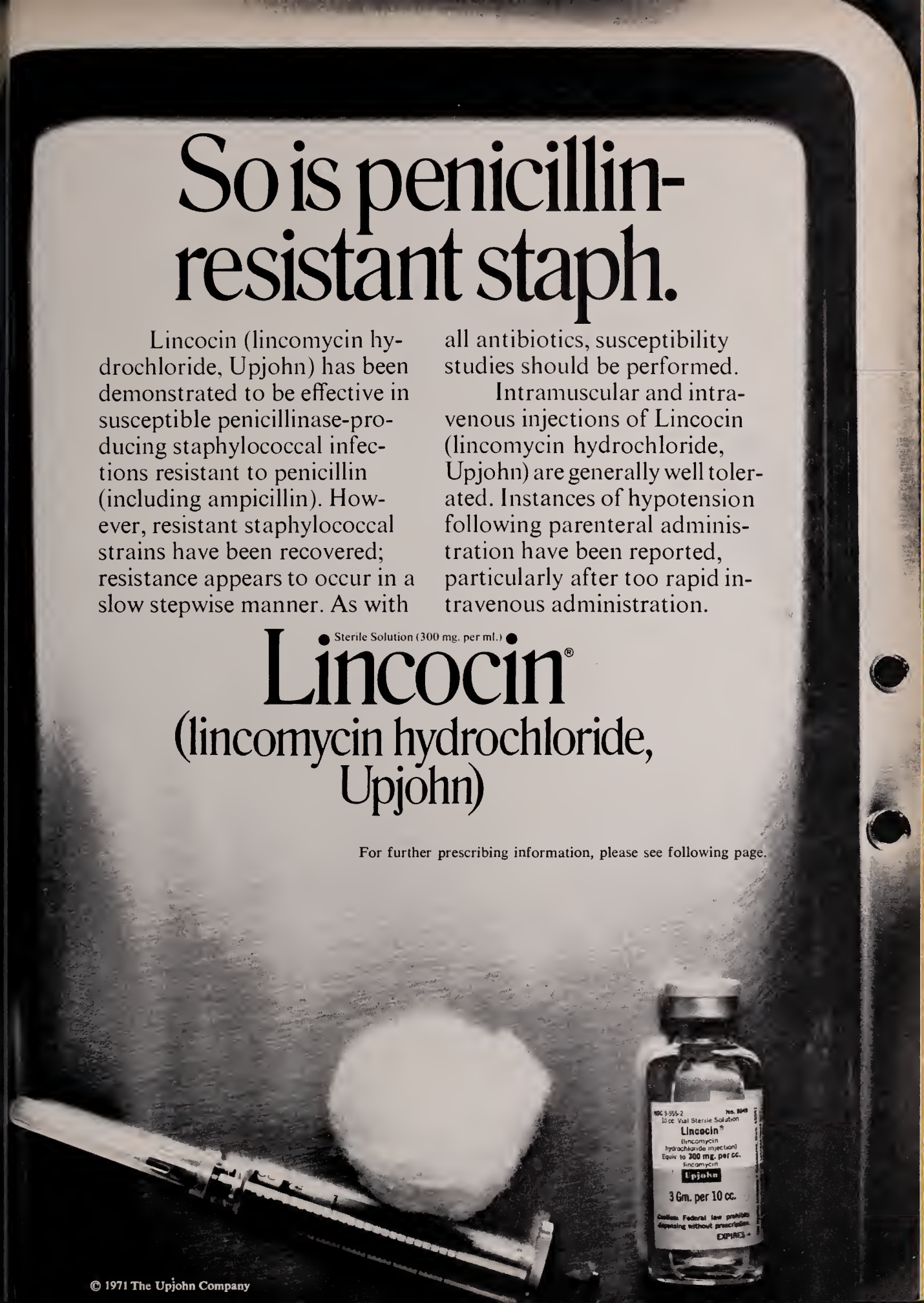
Lincocin (lincomycin hydrochloride, Upjohn) has been demonstrated to be effective in susceptible penicillinase-producing staphylococcal infections resistant to penicillin (including ampicillin). However, resistant staphylococcal strains have been recovered; resistance appears to occur in a slow stepwise manner. As with all antibiotics, susceptibility studies should be performed.

Intramuscular and intravenous injections of Lincocin (lincomycin hydrochloride, Upjohn) are generally well tolerated. Instances of hypotension following parenteral administration have been reported, particularly after too rapid intravenous administration.

Sterile Solution (300 mg. per ml.)

Lincocin®
(lincomycin hydrochloride, Upjohn)

For further prescribing information, please see following page.



© 1971 The Upjohn Company

Sterile Solution (300 mg. per ml.)

Lincocin®

(lincomycin hydrochloride, Upjohn) for respiratory tract, skin, soft-tissue, and bone infections due to susceptible streptococci, pneumococci, and staphyloco

Each preparation contains:	Lincomycin hydrochloride monohydrate equivalent to lincomycin base
250 mg. Pediatric Capsule	250 mg.
500 mg. Capsule	500 mg.
*Sterile Solution per 1 ml.	300 mg.
Syrup per 5 ml.	250 mg.

*Contains also: Benzyl Alcohol 9 mg.; and, Water for Injection—q.s.

An antibiotic chemically distinct from others available, indicated in infections due to susceptible strains of staphylococci, pneumococci, and streptococci. *In vitro* susceptibility studies should be performed.

CONTRAINDICATIONS: History of prior hypersensitivity to Lincocin (lincomycin hydrochloride). Not indicated in the treatment of viral or minor bacterial infections.

WARNINGS: Cases of severe and persistent diarrhea have been reported and at times drug discontinuance has been necessary. This diarrhea has been occasionally associated with blood and mucus and at times has resulted in acute colitis. This reaction usually has been associated with oral therapy, but occasionally has been reported following parenteral therapy. Although cross sensitivity to other antibiotics has not been demonstrated, make careful inquiry concerning previous allergies or sensitivities to drugs. Safety for use in pregnancy has not been established and Lincocin is not indicated in the newborn. Reduce dose 25 to 30% in patients with severe impairment of renal function.

PRECAUTIONS: Like any drug, Lincocin should be used with caution in patients having a history of asthma or significant allergies. Overgrowth of nonsusceptible organisms, particularly yeasts, may occur and require appropriate measures. Patients with pre-existing monilial infections requiring Lincocin therapy should be given concomitant antimonilial treatment. During prolonged Lincocin therapy, periodic liver function studies and blood counts should be performed. Not recommended (inadequate data) in patients with pre-existing liver disease unless special clinical circumstances indicate. Continue treatment of β-hemolytic streptococci infection for ten days to diminish likelihood of rheumatic fever or glomerulonephritis.

ADVERSE REACTIONS: *Gastrointestinal*—Glossitis, stomatitis, nausea, vomiting. Persistent diarrhea, enterocolitis, and pruritus ani. *Hemopoietic*—Neutropenia, leukopenia, agranulocytosis, and thrombocytopenic purpura have been reported. *Hypersensitivity reactions*—Hypersensitivity reactions such as angioneurotic edema, serum sickness, and anaphylaxis have been reported, sometimes in patients sensitive to penicillin. If allergic reaction occurs, discontinue drug. Have epinephrine, corticosteroids, and antihistamines available for emergency treatment. *Skin and mucous membranes*—Skin rashes, urticaria, vaginitis, and rare instances of exfoliative and vesiculobullous dermatitis have been reported. *Liver*—Although no direct relationship to liver dysfunction is established, jaundice and abnormal liver function tests (particularly serum transaminase) have been observed in a few instances.



Cardiovascular—Instances of hypot sion following parenteral administrat have been reported, particularly after rapid I.V. administration. Rare instan of cardiopulmonary arrest have been ported after too rapid I.V. administrati If 4.0 grams or more administered I. dilute in 500 ml. of fluid and adminis no faster than 100 ml. per hour. *Lo reactions*—Excellent local tolerance de onstrated to intramuscularly administe Lincocin. Reports of pain following jection have been infrequent. Intra nous administration of Lincocin in 2 to 500 ml. of 5% glucose in distil water or normal saline has produced local irritation or phlebitis.

HOW SUPPLIED: *250 mg. and 500 r* Capsules—bottles of 24 and 100.

Sterile Solution, 300 mg. per ml.—2 c 10 ml. vials and 2 ml. syringe.

Syrup, 250 mg. per 5 ml.—60 ml. and p bottles.

For additional product information, c sult the package insert or see your Upj representative.

JA71-1203 MED B-5-SR (KZI

The Upjohn Company
Kalamazoo
Michigan 49001

Upjoh

Laboratory Letter

A Few Facts On Fats

Briefly, the facts on fats are these. At least five lipid disorders exist. Each has either a high cholesterol or high triglyceride. And each carries its own symptoms, has its own outlook, and responds differently to diets or drugs. All, and here is this letter's gist, can usually be defined by three tests—cholesterol, triglyceride, and lipoprotein electrophoresis—and your knowledge of the patient's past and present state.

But how, you may ask, should I investigate patients in whom I suspect a lipid disorder? We suggest you first order a cholesterol and triglyceride, especially if you spot a milky or turbid plasma or serum. If both tests are normal, stop. Your patient does not have a hyperlipoproteinemia. If either test is up, however, request a lipoprotein eletrophoresis.

Once you have the three test results, consult the list below and try to categorize your patient. Or, if you prefer, we will interpret results for you. In any case, we believe this list will help you treat your patient and to predict his prognosis.

Type	Serum	Chol.	Trigly.	Electrophoresis	Food Fat	Induction Carbohydrates	Clinical Information
I	milky	normal	high	chylomicron band; other lipoproteins down	yes	no	Rarest type; occurs in children and causes bouts of abdominal pain and xanthomas; to treat, limit fats to 20% of calories.
II	clear	high	normal	beta-lipoprotein up	yes	no	Most common type; patients may have xanthomas in tendons and family history of coronaries before 50; tend to have premature infarcts; low cholesterol diets and lipid lowering drugs help only if condition detected early.
III	clear	high	high	pre-beta and beta-lipoproteins up	no	yes	Uncommon; patients may have xanthomas in palms, but often coronary disease first sign. Treat with balanced diet of fat and carbohydrates with low cholesterol intake. Atromid-S also effective.
IV	clear	high or normal	high	pre-beta lipoprotein up	no	yes	Fairly common in overweight patients with mild diabetes; men with this type may have infarcts before forty. Treat with high-fat, low-carbohydrate, low-calorie diet.
V	turbid or milky	high	high	chylomicron band; pre-beta-lipoproteins up	yes	yes	May present as abdominal pain in late teens or may be secondary to insulin-dependent diabetes, pancreatitis, or alcoholism. Treat with high-protein, low-calorie diet.

Richard L. Reece, M.D.
Minneapolis, Minnesota

Minnesota State Board of Medical Examiners

Notice is hereby given that a public hearing will be held pursuant to Minnesota Statutes, Section 15.0412, subd. 4, in the above-entitled matter in Room 496, Lowry Medical Arts Building, Saint Paul, Minnesota, on Saturday, November 6, 1971, commencing at eleven o'clock a.m., and continuing until all representatives of associations or other interested groups or persons have had an opportunity to be heard concerning the repeal and amendments to the rules captioned above by submitting either oral or written data, statements or arguments. Statements or briefs may be submitted without appearing at the hearing.

A copy of the proposed rules is listed below:

By Bror F. Pearson, M.D.
Secretary-Treasurer

Proposed Amendment to Rule ME 1(c)

It is proposed that Rule ME 1(c) be amended so as to read as follows:
"(c) 'Narcotics' as used in MSA, Sections 147.021, subd. 1(1) and 147.031, subd. 2, shall have the meaning ascribed to the term 'narcotic drugs' by applicable federal and state statutes and Rules and Regulations adopted thereunder."

Proposed Repeal of Rule ME 1(h)

It is proposed that Rule ME 1(h) be repealed.

Proposed Amendment to Rule ME 1(i)

It is proposed that Rule ME 1(i) be renumbered so as to be designated Rule ME 1(h).

Proposed Amendment to Rule ME 1(j)

It is proposed that Rule ME 1(j) be renumbered so as to be designated Rule ME 1(i).

Proposed Amendment to Rule ME 2(b) (3)

It is proposed that Rule ME 2(b) (3) be amended by adding thereto the following sentence: "If the applicant, at the time of making his application, has not yet received such certificate, he may submit the same to the Board at any time prior to licensure."

Proposed Amendment to Rule ME 2(c)

It is proposed that Rule ME 2(c) be amended by striking and deleting all of the same and by substituting the following in lieu and in place thereof:
"(c) An applicant who has passed the written examination in the clinical sciences of the National Board of Medical Examiners or The Federation of State Medical Boards of the United States, Inc. shall include in his application, in addition to the information required under ME 2(b), evidence satisfactory to the Board that within three years before or five years after being granted the degree of Doctor of Medicine, or Doctor of Osteopathy, the applicant has satisfactorily passed the examination in the clinical sciences which is prepared, administered and graded in accordance with the provisions of MSA, § 147.02. The Board may, but shall not be required to, recognize and approve the results of such examination in the clinical sciences."

Proposed Amendment to Rule ME 3(a)

It is proposed that Rule ME 3(a) be amended by striking and deleting all of the same and by substituting the following in lieu and in place thereof:
"(a) A written examination shall be given in the clinical sciences (including, but not limited to, surgery, medicine, obstetrics, gynecology, and such other branches as the Board may from time to time determine) and in order to determine clinical competence. Such written examination in the clinical sciences and in order to determine clinical competence may be prepared, administered and graded by the Board or by the National Board of Medical Examiners, or prepared and graded by the National Board of Medical Examiners or by The Federation of State Medical Boards of the United States, Inc. and administered by the Board."

Proposed Amendment to Rule ME 3(c)

It is proposed that Rule ME 3(c) be amended by striking and deleting all of the same and by substituting the following in lieu and in place thereof:
"(c) A grade of 75 shall be the passing grade on all examinations graded by the Board, and a weighted average grade of 75 shall be the passing grade on all examinations graded by the National Board of Medical Examiners or The Federation of State Medical Boards of the United States, Inc. If an applicant falls below 75 in more than two subjects on an examination graded by the Board, or below the weighted average grade of 75 in more than two subjects on examinations graded by National Board of Medical Examiners or The Federation of State Medical Boards of the United States, Inc., it shall constitute a failure and require that the applicant retake the entire examination with passing grades in order to be eligible for licensure. An applicant failing not more than two subjects may retake those subjects at the next examination and upon receiving a passing grade in each, may be eligible for licensure."

Classified Advertisements

Classified advertising rates are thirty (30) cents a word; minimum monthly charge $7.50; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

ARE YOU TIRED OF THE SMOG, traffic congestion, sociological problems, crime and other irritations which have become part of today's urban living? Well then DISCOVER WATERTOWN, WISCONSIN. Exchange all the big city unpleasantries for the peaceful environment and easy going pace of a residential city. Watertown, a progressive community, is ideally located equi-distant between Milwaukee and Madison in southeastern Wisconsin's lake district. The community has a trade (and medical practice) area serving 40 - 50,000 people. Many new schools, parks, trees and recreational opportunities. A stable economy. Our new Community Health Care Center with its beautiful 110 bed general hospital, connecting (but separate) 24 unit Medical-Dental Office Building (choice of suites still available), and connecting 130 bed Nursing Home, was completed in the Spring of 1971. WE URGENTLY NEED another Internist, an Otolaryngologist, an Opthalmologist, Obstetrician-Gynecologists, Pediatricians and Family Practitioners to join existing medical staff. An immediate succesful practice assured. Excellent rapport with the University of Wisconsin Medical School at Madison, and the Medical College of Wisconsin (formerly Marquette University School of Medicine) at Milwaukee. Medical Staff leading and supporting recruitment effort. Write or call Dr. Paul Glunz, Watertown Memorial Hospital, Watertown, Wis., 53094. Telephone 414-261-4210.

INTERNIST WANTED—Board Certified or Eligible. Join two Internists, Radiologists, General Surgeon and EENT physician (all Mayo trained and Certified). Modern clinic building located in University city having three fully equipped hospitals. Population 100,000. For further information write Green Bay Clinic, 123 N. Military Ave., Green Bay, Wis. 54303.

GENERAL PRACTITIONER wanted to take over busy and well established practice. Good nearby hospitals. Little or no capital investment. Excellent office facilities. Write or call A. M. Jensen M.D., Telephones: Office (612) 328-5223, Res. 328-4428. Brownton, Minnesota 55312.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul 55101.

SPACIOUS 5 ROOM office for rent, fully equipped 100 MA X-ray, laboratory etc., in working condition, also minor surgery. Will introduce clientel. There is space for 2 MDs. Location: Minneapolis Lake Calhoun area. Phone: Dr. Pone, 825-0700.

WANTED NOW: General Practitioner and a Surgeon to join our three-doctor Clinic in Northwest Wisconsin Resort, Forest and Retirement Area Town of 2,400 with a patient population of 25,000. Fully equipped modern Clinic building, with new accredited 50-bed Hospital and 50-bed extended care nursing home. Deer, ducks, partridge and fish 5 minutes away. Generous salary commensurate with training and experience the first year, then full partnership. Brochure with maps and photos upon request. Call collect or write L. J. Olson, M. D., Spooner Clinic Ltd., Spooner, Wisconsin 54801, telephone 715-635-2151.

INTERNIST RETURNING to Academic Medicine. Lease, with or without furnishings incl., X-ray and lab available. 980 square feet in Meadowbrook Medical Bldg. 920-9797 or 935-0768.

TWO GENERAL PRACTITIONERS and internist wanted for 4 man GP group with Board surgeon in NE Minnesota; accredited hospital with radiologist, pathologist and internist services; new clinic; indoor ice arena, hunting, fishing, skiing, canoeing, $25,000 to $28 000 start to $36,000 to $39,000 after four years; full partner six months; no investment; equal call & immediate workload, primarily family practice with OB and minor surgery. Write Medical Director, Community Clinic, Two Harbors, Minnesota 55616.

AVAILABLE—Young married G.P. with some surgical experience. Deferment not needed. Write Minnesota Medicine, 462, 375 Jackson St., St. Paul 55101.

POSITIONS WANTED. Have talent. Will travel, December graduates of the MLA (CLA) program of the Hibbing Area Technical Institute will fulfill the needs of your laboratory. Contact: Charlotte Sandstrom, Hibbing Area Technical Institute, Hibbing Minnesota. Phone: 218-262-3824.

(Continued to Page 950.)







T_4 IS THE PREDICTABLE HORMONE BECAUSE IT LOVES PROTEIN.

SYNTHROID® (sodium levothyroxine) is pure synthetic T_4, the major circulating thyroid hormone. It is reliable to use because of its affinity for protein-binding sites in the blood. T_3 is more fickle. Sometimes it binds. Sometimes it doesn't. T_4 more *predictably* binds to protein.

Synthroid®
(sodium levothyroxine)

ALL THYROID-FUNCTION TESTS ARE USEFUL IN MONITORING SYNTHROID THERAPY

No calculations are needed, test interpretation is simple.

Any of the commonly used T_4 thyroid function tests (P.B.I., T_4 By Column, Murphy-Pattee, Free Thyroxine) are useful in monitoring patients on T_4 because they *all* measure T_4. Patients on SYNTHROID are thereby easy to monitor because their results will fall within predictable, elevated test ranges. Of course, clinical assessment is the best criterion of the thyroid status of the drug-treated patient.

TEST	HYPOTHYROID	SYNTHROID THERAPEUTIC NORMAL
P.B.I.	Less than 4 mcg %	6-10 mcg %
T_4 By Column	Less than 3 mcg %	7-9 mcg %
T_3 (Resin)	Less than 25%	27-35%
T_3 (Red Cell)	Less than 11%	11.5-18%
Free Thyroxine	Less than 0.7 nanograms %	0.7-2.5 nanograms %
Murphy-Pattee	Less than 2.9 mcg %	4-11 mcg %

TWO GOOD REASONS WHY THE ROAD TO NORMALIZED THYROID STATUS IS SO SMOOTH FOR THE SYNTHROID PATIENT.

(1) The onset of action of T_4 is gradual. It has a long in vivo "half-life" of over six days. (Occasional missed doses or accidental double-doses are of les concern because of this factor)[1]; (2) since SYNTHROID contains on T_4, the potential for metabolic surges traceable to more potent iodides (T_3) is eliminated.



AS WITH ANY THYROID PREPARATION, CAUTIOUS OBSERVATION OF THE PATIENT DURING THE BEGINNING OF THERAPY WILL ALERT THE PHYSICIAN TO ANY UNTOWARD EFFECTS.

Side effects, when they do occur, are related to excessive dosage. Caution should be exercised in administering the drug to patients with cardiovascular disease. Read the accompanying prescribing information for additional data or write Flint Laboratories.

Choose the Smooth Road ...to thyroid replacement therapy





PATIENTS CAN BE SUCCESSFULLY MAINTAINED ON A DRUG CONTAINING THYROXINE ALONE.

Thyroxine (T_4) is, as you know, the major circulating hormone produced by the thyroid gland. T_3 is also produced, in smaller amounts, and is active at the cellular level. For years it has been a working hypothesis among endocrinologists that T_4 is converted by the body to T_3. In 1970 this process, called "deiodination," was demonstrated by Sterling and Braverman[2]. T_4 does convert to T_3, though the precise quantities are still being studied.

The conversion has been clinically demonstrated during the administration of T_4 to athyrotic patients. Their thyroid status is normalized on SYNTHROID alone, yet the presence of T_3 in these patients has been clearly shown.

WHY DOES SYNTHROID COST LESS THAN SYNTHETIC DRUGS CONTAINING T_3?

Very simple. T_3 costs more to make synthetically than does T_4. So it is economically necessary for a synthetic thyroid medication containing T_3 to cost more than one containing T_4 alone. Synthetic combinations cost patients nearly 50% more than SYNTHROID[4] because the T_3 costs more to start with; also there is the additional expense of formulating a tablet containing two active ingredients.

1. Latiolais, C. J., and Berry, C. C.: Misuse of Prescription Medications by Outpatients, *Drug Intelligence & Clin. Pharm.* 3:270-7, 1969.
2. Braverman, L. E., Ingbar, S. H., and Sterling, K.: Conversion of Thyroxine (T4) to Triiodothyronine (T3) in Athyreotic Human Subjects, *J. Clin. Invest.* 49:855-64, 1970.
3. American Druggist BLUEBOOK, March, 1971.

THE FACTS ARE CLEAR AND HERE IS OUR OFFER.

FACTS:
Synthetic thyroid drugs are an improvement over animal gland products. Patients, even athyrotic ones, can be completely maintained on SYNTHROID (T_4) alone. Thyroid function tests are easy to interpret since they are *predictably* elevated when the patient adheres to SYNTHROID. Of all synthetic thyroid drugs, SYNTHROID is the most economical to the patient.

A

OFFER:
Free TAB-MINDER medication dispensers to start or convert all your hypothyroid patients to SYNTHROID. Free information to physicians on role of thyroid function tests in a new booklet titled: "Guideposts to Thyroid Therapy." Ask us.

Name

Address

City State Zip

Indications: SYNTHROID (sodium levothyroxine) is specific replacement therapy for diminished or absent thyroid function resulting from primary or secondary atrophy of the gland, congenital defect, surgery, excessive radiation, or antithyroid drugs. Indications for SYNTHROID (sodium levothyroxine) **Tablets** include myxedema, hypothyroidism without myxedema, hypothyroidism in pregnancy, pediatric and geriatric hypothyroidism, hypopituitary hypothyroidism, simple (nontoxic) goiter, and reproductive disorders associated with hypothyroidism. SYNTHROID (sodium levothyroxine) **for Injection** is indicated for intravenous use in myxedematous coma and other thyroid dysfunctions where rapid replacement of the hormone is required. The injection is also indicated for intramuscular use in cases where the oral route is suspect or contraindicated due to existing conditions or to absorption defects, and when a rapid onset of effect is not desired.

Precautions: As with other thyroid preparations, an overdosage may cause diarrhea or cramps, nervousness, tremors, tachycardia, vomiting and continued weight loss. These effects may begin after four or five days or may not become apparent for one to three weeks. Patients receiving the drug should be observed closely for signs of thyrotoxicosis. If indications of overdosage appear, discontinue medication for 2-6 days, then resume at a lower dosage level. In patients with diabetes mellitus, careful observations should be made for changes in insulin or other antidiabetic drug dosage requirements. If hypothyroidism is accompanied by adrenal insufficiency, as Addison's Disease (chronic subcortical insufficiency), Simmonds's Disease (panhypopituitarism) or Cushing's syndrome (hyperadrenalism), these dysfunctions must be corrected prior to and during SYNTHROID (sodium levothyroxine) administration. The drug should be administered with caution to patients with cardiovascular disease; development of chest pains or other aggravations of cardiovascular disease requires a reduction in dosage.

Contraindications: Thyrotoxicosis, acute myocardial infarction. **Side effects:** The effects of SYNTHROID (sodium levothyroxine) therapy are slow in being manifested. Side effects, when they do occur, are secondary to increased rates of body metabolism; sweating, heart palpitations with or without pain, leg cramps, and weight loss. Diarrhea, vomiting, and nervousness have also been observed. Myxedematous patients with heart disease have died from abrupt increases in dosage of thyroid drugs. Careful observation of the patient during the beginning of any thyroid therapy will alert the physician to any untoward effects.

In most cases with side effects, a reduction of dosage followed by a more gradual adjustment upward will result in a more accurate indication of the patient's dosage requirements without the appearance of side effects.

Dosage and Administration: The activity of a 0.1 mg. SYNTHROID (sodium levothyroxine) TABLET is equivalent to approximately one grain thyroid, U.S.P. Administer SYNTHROID tablets as a single daily dose, preferably after breakfast. In hypothyroidism without myxedema, the usual initial adult dose is 0.1 mg. daily, and may be increased by 0.1 mg. every 30 days until proper metabolic balance is attained. Clinical evaluation should be made monthly and PBI measurements about every 90 days. Final maintenance dosage will usually range from 0.2-0.4 mg. daily. In adult myxedema, starting dose should be 0.025 mg. daily. The dose may be increased to 0.05 mg. after two weeks and to 0.1 mg. at the end of a second two weeks. The daily dose may be further increased at two-month intervals by 0.1 mg. until the optimum maintenance dose is reached (0.1-1.0 mg. daily).

Supplied: Tablets: 0.025 mg., 0.05 mg., 0.1 mg., 0.15 mg., 0.2 mg., 0.3 mg., 0.5 mg., scored and color-coded, in bottles of 100, 500, and 1000. Injection: 500 mcg. lyophilized active ingredient and 10 mg. of Mannitol, N.F., in 10 ml. single-dose vial, with 5 ml. vial of Sodium Chloride Injection, U.S.P., as a diluent. SYNTHROID (sodium levothyroxine) **for Injection** may be administered intravenously utilizing 200-400 mcg. of a solution containing 100 mcg. per ml. If significant improvement is not shown the following day, a repeat injection of 100-200 mcg. may be given.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Morton Grove, Illinois 60053

Classified Advertisements

(Continued from Page 947.)

GENERAL PHYSICIAN wanted for locum tenens, start as soon as possible, for two to six months with permanent placement assured if mutually agreeable, small group practice (4) in NE Minnesota. Equitable call schedule. Write Medical Director, Community Clinic, Two Harbors, Minnesota 55616.

PSYCHIATRIC RESIDENCIES—Excellent, approved psychiatric training; both demanding and clinically rich with a stimulating, well-balanced program. Affiliated with Michigan State University's College of Human Medicine. The setting is a culturally satisfying community; the serene, scenic Grand Traverse Bay area. Three year plan: $12,215 to $13,885; five-year plan: $13,927 to $26,121. Contact Dr. Paul E. Kauffman, Director of Psychiatric Training, Room (166), Traverse City State Hospital, Traverse City, Michigan 49684. Phone: (616) 947-5550. An equal opportunity employer.

MOST DELUXE ARIZONA style rambler on Mississippi River in north suburb of Minneapolis. Too many features to mention. $125,000.00, owner will finance. Call 537-6533 weekdays for appointment, Mr. Kirchner.

University of Minnesota

Office of Postgraduate Medical Education—Medical School

November

November 11-13 .....Refraction—for Non-Ophthalmologists (limited enrollment)

November 12-14 .....Second Annual Kidney Foundation Symposium

November 18-20 .....Application of the Health Science Computers in the Community Hospital

December

December 2-4 .....Clinic Management for Doctors

December 6-7 .....Practical Ophthalmology for Non-Ophthalmologists

For further Information Concerning the Above Listed Programs and Opportions Contact: Office of Postgraduate Medical Education, Box 193 Health Sciences Center, University of Minnesota, Minneapolis, Minnesota 55455.

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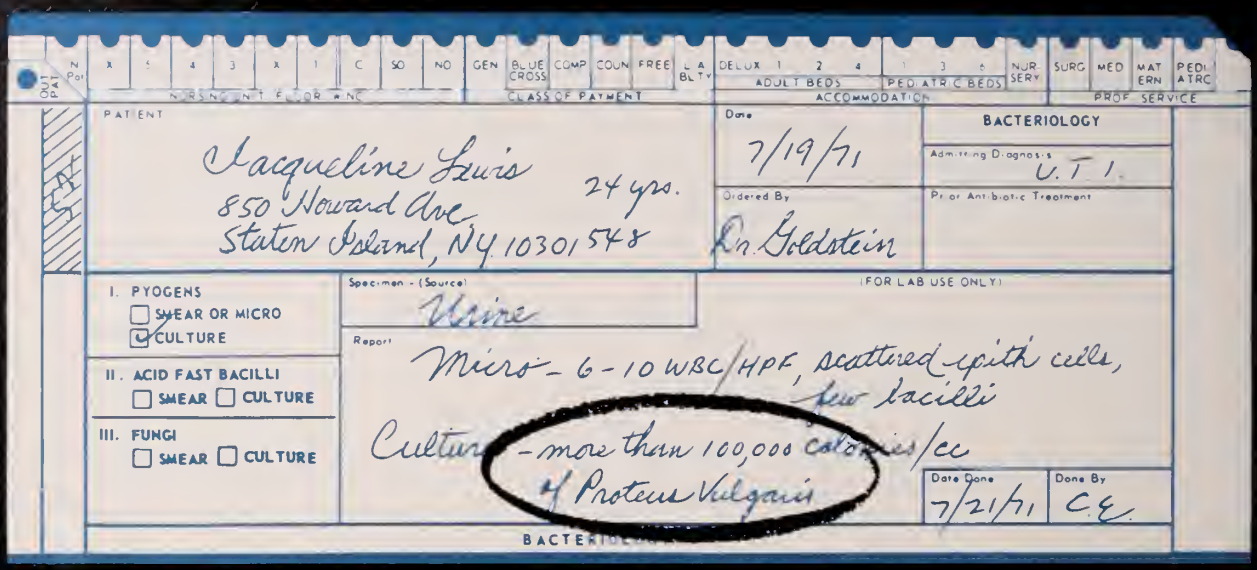
A gratifying announcement about Empirin® Compound with Codeine



You may now specify up to five refills within six months when you prescribe Empirin Compound with Codeine (unless restricted by state law).

It is significant in this era of increased regulation, that Empirin Compound with Codeine has been placed in a less restrictive category. You may now wish to consider Empirin with Codeine even more frequently for its predictable analgesia in acute or protracted pain of moderate to severe intensity.

Empirin Compound with Codeine No. 3 contains codeine phosphate* (32.4 mg.) gr. ½. No. 4 contains codeine phosphate* (64.8 mg.) gr. 1. *(Warning—may be habit-forming.) Each tablet also contains: aspirin gr. 3½, phenacetin gr. 2½, caffeine gr. ½.



PATIENT
Jacqueline Louis
850 Howard Ave
Staten Island, NY 10301 548
24 yrs.

Date
7/19/71

BACTERIOLOGY

Admitting Diagnosis
U. T. I.

Ordered By
Dr. Goldstein

Prior Antibiotic Treatment

(FOR LAB USE ONLY)

I. PYOGENS
☐ SMEAR OR MICRO
☑ CULTURE

II. ACID FAST BACILLI
☐ SMEAR ☐ CULTURE

III. FUNGI
☐ SMEAR ☐ CULTURE

Specimen - (Source)
Urine

Report
Micro - 6-10 WBC/HPF, scattered epith cells, few bacilli
Culture - more than 100,000 colonies/cc
of Proteus Vulgaris

Date Done
7/21/71

Done By
C.E.

BACTERIOLOGY

the choice is clear:

Pyopen®

(sterile disodium carbenicillin)

A serious urinary tract infection...
Proteus vulgaris, confirmed by pure culture. Fortunately, the strain proves sensitive to carbenicillin and the patient is not allergic to penicillins. The choice is clear: Pyopen.

Unlike other antibiotics currently available for the treatment of Gram-negative sepsis, there are no reports of nephrotoxicity or ototoxicity with Pyopen therapy. Particularly valuable in urinary infections, because of its exceptionally high urine levels, its effectiveness against *Ps. aeruginosa* and *Proteus* species has been amply confirmed by clinical experience and microbiologic studies.

Pyopen is a product of Beecham, the company which pioneered most of today's semi-synthetic penicillins. Your Beecham-Massengill representative would like to give you proof of our dedication to the concept of Total Service.

THE TOTAL SERVICE CONCEPT:
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For additional information about the Beecham-Massengill Total Service Concept see our representative or write to us directly.

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PRESCRIBING INFORMATION **Indications:** Primarily for treatment of infections due to susceptible strains of *Pseudomonas aeruginosa*, *Proteus* species (particularly indole-positive strains), and certain *Escherichia coli*. Clinical effectiveness has been demonstrated in the following infections when due to these organisms: Urinary tract infections; severe systemic infections and septicemia; acute and chronic respiratory infections (while clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis); soft tissue infections. Although PYOPEN (disodium carbenicillin) is indicated primarily in Gram-negative infections, its activity against Gram-positive organisms should be kept in mind when both Gram-positive and Gram-negative organisms are isolated (see Actions). **Note:** During therapy, sensitivity testing should be repeated frequently to detect the possible emergence of resistant organisms. **Actions:** Organisms found to be susceptible *in vitro* include: Gram-Negative Organisms-*Ps. aeruginosa*, *Proteus mirabilis*, *Pr. morganii*, *Pr. rettgeri*, *Pr. vulgaris*, *E. coli*, *Enterobacter* species, *Salmonella* species, *Hemophilus influenzae*, and *Neisseria* species. Gram-Positive Organisms-*Staphylococcus aureus* (nonpenicillinase-producing), *Staph. albus*, *Diplococcus pneumoniae*, Beta-hemolytic streptococci, and *Streptococcus faecalis*. Some newly emerging pathogenic strains of *Herellea*, *Mima*, *Citrobacter*, and *Serratia* have also shown *in vitro* susceptibility. Not stable in the presence of penicillinase. *Klebsiella* species are resistant. Some strains of *Pseudomonas* have developed resistance fairly rapidly. **Contraindications:** Known penicillin allergy. **Warnings:** Serious and occasional fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted and discontinuance of disodium carbenicillin therapy considered, unless the infection is life threatening and only amenable to disodium carbenicillin therapy. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available. **Usage in Pregnancy:** Safety for use in pregnancy has not been established. **Precautions:** As with any other potent agent, it is advisable to check periodically for organ-system dysfunction, including renal, hepatic, and hematopoietic systems, during prolonged therapy. Emergence of resistant organisms, such as *Klebsiella* species and *Serratia* species, which may cause superinfection, should be kept in mind. Each gram contains 4.7 mEq sodium; in patients where sodium restriction is necessary, such as cardiac patients, periodic electrolyte determinations and monitoring of cardiac status should be made. Observe patients with renal impairment for bleeding manifestations and adhere strictly to dosage recommendations. If bleeding manifestations appear, discontinue antibiotic and institute appropriate therapy. As with any penicillin preparation, the possibility of an allergic response, including anaphylaxis, may occur, particularly in a hypersensitive individual. **Administration:** Intramuscular injections should be made well within the body of a relatively large muscle (not into the lower and mid-third of the upper arm), and aspiration is necessary to help avoid inadvertent injection into a blood vessel. May be given by either intravenous injection or intravenous infusion. After reconstitution with Sterile Water for Injection unused portions should be discarded after 24 hours if stored at room temperature, or after 72 hours if refrigerated. **Adverse Reactions:** *Hypersensitivity Reactions*—Skin rashes, eosinophilia, pruritus, urticaria, drug fever, and anaphylactic reactions. *Gastrointestinal Disturbances*—Nausea. *Hemic and Lymphatic Systems*—Hemolytic anemia, thrombocytopenia, leukopenia, neutropenia, in uremic patients receiving high doses (24 gm/day), hemorrhagic manifestations associated with abnormalities of coagulation tests, such as clotting and prothrombin time. *Hepatic and Renal Studies*—SGOT and SGPT elevations have been observed, particularly in children. To date, no clinical manifestations of renal disorders have been demonstrated. *Central Nervous System*—Convulsions or neuromuscular irritability could occur with excessively high serum levels. *Local Reactions*—Pain at the site of injection, sometimes accompanied by induration. Vein Irritation and Thrombophlebitis—particularly when undiluted solution is injected directly into the vein. **How Supplied:** Available in 1 Gm. and 5 Gm. vials.
Before prescribing or administering, see package circular or PDR.

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A family doctor looks at new developments in the pharmaceutical industry. And he speculates on the future.

When I look back at some of my old records, I'm constantly reminded of the changes that have come about in medicine just during the past twenty-five years. Some of the diseases I treated and prayed over in the '40's are found mostly in medical history books now.

Thanks to drug research and development, we've made substantial gains in the control of cardiovascular disease, diabetes, malaria, mental illness, strep and staph infections, meningitis and a long list of ailments. It seems like only yesterday when a diagnosis of pneumonia was almost the kiss of death. Now, with modern medical techniques and drug therapy, we can offer some real help.

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I hear questions about the three billion or so dollars spent by the drug industry in research during the past ten years . . . working on new and better drug products. It does seem like quite a bit of money to spend, and I realize some of it goes into dead ends. That's the problem with research, any research . . . you often don't know where you're going until you get there. I want all the tools I can get to help my patients. I want more drugs and more effective drugs. If they mean less pain, longer lives and more productive careers for those I treat . . . well, that's what really counts.

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Book Reviews

ANATOMY FOR SURGEONS, VOL. 1, THE HEAD AND NECK, 2ND EDITION. Author: W. Henry Hollinshead, Ph.D. Publisher: Hoeber Medical Division, Harper & Row, New York, N.Y. Price: $20.00. Pages 634. Illustrations: 600.

This Anatomy of the Head and Neck is an excellent monograph for the surgeon in clinical practice. The details of complete descriptive anatomy are not included, but anatomical structures and variations are well described and beautifully illustrated with line drawings. This gives the clinical surgeon an opportunity to review the anatomy under consideration and have readily at hand the variations which might be encountered in the course of a surgical operation.

This will be particularly useful to the ophthalmologist and to the otolaryngologist. Chapter 9 deals with Surgery of the Neck which in most circumstances will probably be useful to the surgeon who does goiter surgery and neck dissections.

The illustrations are labeled in chapter sequence so that the first number indicates the chapter and the subsequent numbers indicate the sequence within the chapter. The headings and sub-headings are well placed and the type faces are large enough to be easily read without eye strain.

Carl O. Rice, M.D.
Minneapolis, Minnesota

1970 DRUGS OF CHOICE 1971. W. Modell: C. V. Mosby, St. Louis. 1970. pp. 924, $20.50.

Modell's biennial review of pharmacology is now appearing in its seventh edition, a recurring fixture on the medical scene, a necessary compendium for the practicing physician proverbially too busy to keep himself current by reading the journals. Modell says ". . . the fertile mating of the synthetic chemist and the pharmaceutical manufacturer (has produced) new drugs on the market almost too quickly for the physician to learn the names, to say nothing of distinguishing which were the same drugs with different proprietary names." One wonders in this mating which is the male and which the female, but a moment's reflection resolves this issue: the pharmaceutical manufacturer is the female producing the new drugs. Modell, like all pharmacologists, deplores the use of trade names and, in principle, clinicians agree. But I doubt if any of MINNESOTA MEDICINE'S readers know what DEXTROPROPOXYPHENE HYDROCHLORIDE is—let alone write it on prescription. However, the great majority of our physician readers have prescribed it as DARVON. In deference to us plain old practicing physicians Modell has a second index listing trade names. The Chapter "Principles for the Choice of Drugs" is worth the price of the book.

Reuben Berman, M.D.
Minneapolis, Minnesota

PROCEEDINGS OF THE CENTENNIAL SYMPOSIUM, MANHATTAN EYE, EAR AND THROAT HOSPITAL, VOLUME II—OTOLARYNGOLOGY. Edited by William F. Robbett, M.D. Publication Date: November 1969. Publishers: The C. V. Mosby Company. Price: $27.50.

A symposium was held in New York City from June 3 to 7, 1968, in honor of Manhattan Eye, Ear and Throat Hospital's centennial anniversary. There were 57 contributors to the section on Otolaryngology: specialists in their field from all parts of the United States and a number of foreign countries.

The book is divided into eight sections: Otology, Tympanoplasty, Facial Nerve, Surgery of Cochlear Hydrops, Recent Techniques in Otolaryngology, Plastic and Reconstructive Surgery, Head and Neck Surgery, and Laryngeal Surgery.

The section on Otology begins with a symposium on stapes surgery, discussion problems such as the choice of candidates for surgery, techniques of stapedectomy, and the types of prostheses used, blood and fragments of footplate in the vestibule, fistula and granuloma formation, and the future development of stapes surgery. Also in this section are discussions on electronystagmography in clinical practice, translabyrinthine section of the eighth cranial nerve, and tomography of the middle ear.

Decompression of the endolymphatic sac, cryosurgery, and ultrasound are all discussed in the surgical treatment of cochlear hydrops. Recent techniques in otolaryngology include cryosurgery, diagnostic radiologic techniques, vidian neurectomy and transsphenoidal hypophysectomy.

The section on plastic and reconstructive surgery has three excellent chapters on congenital and acquired auricular deformities. Also discussed are prosthetic aids in the treatment of facial fractures and mandibular resections, bone grafts to the nose, treatment of soft tissue injuries, and secondary and tertiary correction of postrhinoplastic deformities. Functional neck dissection, problems in classification of parotid tumors, and reconstructive procedures in radical head and neck surgery are the topics in the section of head and neck surgery.

In the section on laryngeal surgery there are three well-organized panel discussions on combined radiation and surgery in carcinoma of the larynx, conservation surgery for carcinoma of the larynx, and radiation or surgery in certain tumors of the larynx. The remaining portion of this section includes surgery for vocal rehabilitation after laryngectomy, microsurgery of the larynx, and functional restoration of the larynx.

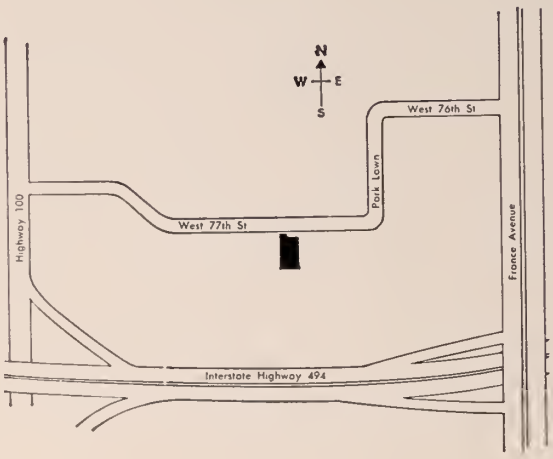
As can be readily seen, this symposium includes current medical topics of high interest. Each contributor had only a limited time in which to present his topic but does so in a well-organized manner. This book would be a valuable addition to the otolaryngologist's library because it discusses up-to-date trends in the field of otolaryngology.

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Indications

Pre-Sate (chlorphentermine hydrochloride) is indicated in exogenous obesity, as a short term (i.e. several weeks) adjunct in a regimen of weight reduction based upon caloric restriction.

Contraindications

Glaucoma, hyperthyroidism, pheochromocytoma, hypersensitivity to sympathomimetic amines, and agitated states. Pre-Sate (chlorphentermine hydrochloride) is also contraindicated in patients with a history of drug abuse or symptomatic cardiovascular disease of the following types: advanced arteriosclerosis, severe coronary artery disease, moderate to severe hypertension, or cardiac conduction abnormalities with danger of arrhythmias. The drug is also contraindicated during or within 14 days following administration of monamine oxidase inhibitors, since hypertensive crises may result.

Warnings

When weight loss is unsatisfactory the recommended dosage should not be increased in an attempt to obtain increased anorexigenic effect; discontinue the drug. Tolerance to the anorectic effect may develop. Drowsiness or stimulation may occur and may impair ability to engage in potentially hazardous activities such as operating machinery, driving a motor vehicle, or performing tasks requiring precision work or critical judgment. Therefore, such patients should be cautioned accordingly. Caution must be exercised if Pre-Sate (chlorphentermine hydrochloride) is used concomitantly with other central nervous system stimulants. There have been reports of pulmonary hypertension in patients who received related drugs.

Drug Dependence Drugs of this type have a potential for abuse. Patients have been known to increase the intake of drugs of this type to many times the dosages recommended. In long-term controlled studies with the high dosages of Pre-Sate, abrupt cessation did not result in symptoms of withdrawal.

Usage In Pregnancy The safety of Pre-Sate (chlorphentermine hydrochloride) in human pregnancy has not yet been clearly established. The use of anorectic agents by women who are or who may become pregnant, and especially those in the first trimester of pregnancy, requires that the potential benefit be weighed against the possible hazard to mother and child. Use of the drug during lactation is not recommended. Mammalian reproductive and teratogenic studies with high multiples of the human dose have been negative.

Usage In Children Not recommended for use in children under 12 years of age.

Precautions

In patients with diabetes mellitus there may be alteration of insulin requirements due to dietary restrictions and weight loss. Pre-Sate (chlorphentermine hydrochloride) should be used with caution when obesity complicates the management of patients with mild to moderate cardiovascular disease or diabetes mellitus, and only when dietary restriction alone has been unsuccessful in achieving desired weight reduction. In prescribing this drug for obese patients in whom it is undesirable to introduce CNS stimulation or pressor effect, the physician should be alert to the individual who may be overly sensitive to this drug. Psychologic disturbances have been reported in patients who concomitantly receive an anorectic agent and a restrictive dietary regimen.

Adverse Reactions

Central Nervous System: When CNS side effects occur, they are most often manifested as drowsiness or sedation or overstimulation and restlessness. Insomnia, dizziness, headache, euphoria, dysphoria, and tremor may also occur. Psychotic episodes, although rare, have been noted even at recommended doses. **Cardiovascular:** tachycardia, palpitation, elevation of blood pressure. **Gastrointestinal:** nausea and vomiting, diarrhea, unpleasant taste, constipation. **Endocrine:** changes in libido, impotence. **Autonomic:** dryness of mouth, sweating, mydriasis. **Allergic:** urticaria. **Genitourinary:** diuresis and, rarely, difficulty in initiating micturition. **Others:** Paresthesias, sural spasms.

Dosage and Administration

The recommended adult daily dose of Pre-Sate (chlorphentermine hydrochloride) is one tablet (equivalent to 65 mg chlorphentermine base) taken after the first meal of the day. Use in children under 12 not recommended.

Overdosage

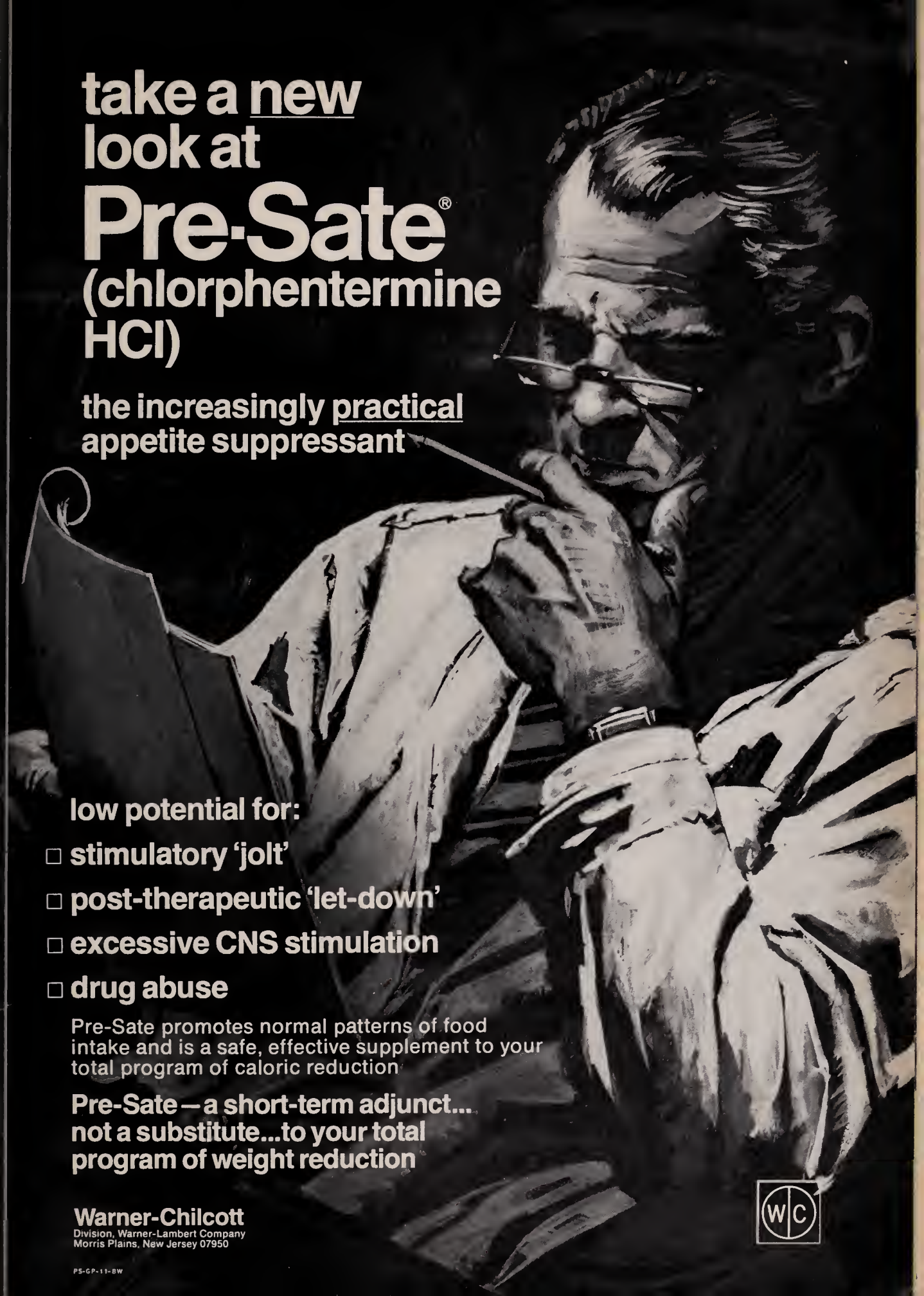
Manifestations: Restlessness, confusion, assaultiveness, hallucinations, panic states, and hyperpyrexia may be manifestations of acute intoxication with anorectic agents. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension, or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management: Management of acute intoxication with sympathomimetic amines is largely symptomatic and supportive and often includes sedation with a barbiturate. If hypertension is marked, the use of a nitrate or rapidly acting alpha-receptor blocking agent should be considered. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

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DECEMBER, 1971

Patients fell asleep quickly

Dalmane (flurazepam HCl) 30 mg reduced awake time—both before and after falling asleep - by fifty percent of pretreatment values in patients with insomnia.[1,2]

Two sleep laboratory studies recently confirmed findings of earlier studies of this type, namely, that Dalmane 30 mg was effective in patients who had trouble falling asleep, staying asleep or both. One 30-mg capsule of Dalmane usually induced sleep within 22 minutes, decreased the number of awakenings and the wake time after the onset of sleep, and provided 7 to 8 hours of sleep without need to repeat dosage during the night.

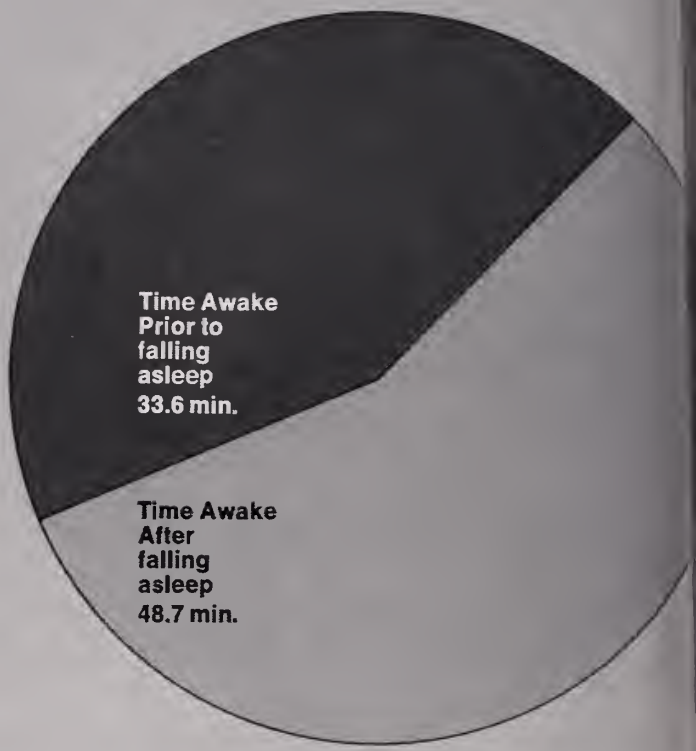
These studies utilized identical protocols and included eight insomniac patients. Sleep laboratory measurements in a limited number of patients are derived from all-night electro-encephalographic, electro-oculographic and electromyographic tracings. Unlike traditional methods of evaluation, they are quantitative, reproducible and projectable to large numbers of subjects.

Results shown represent average values in all subjects for the three consecutive nights of placebo administration prior to Dalmane therapy and the seven consecutive nights on Dalmane 30 mg.

Dalmane is also relatively safe, as reported in clinical studies. Instances of morning "hang-over" have been relatively infrequent; paradoxical reactions (excitement) and hypotension have been rare. Dizziness, drowsiness, lightheadedness and the like were the side effects noted most frequently, particularly in the elderly or debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

References: 1. Frost, J. D., Jr.: "A System for Automatically Analyzing Sleep," Scientific Exhibit presented at Clinical Convention, A.M.A., Boston, Nov. 29-Dec. 2, 1970, and Aerospace M.A., Houston, April 26-29, 1971.
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley, N.J.

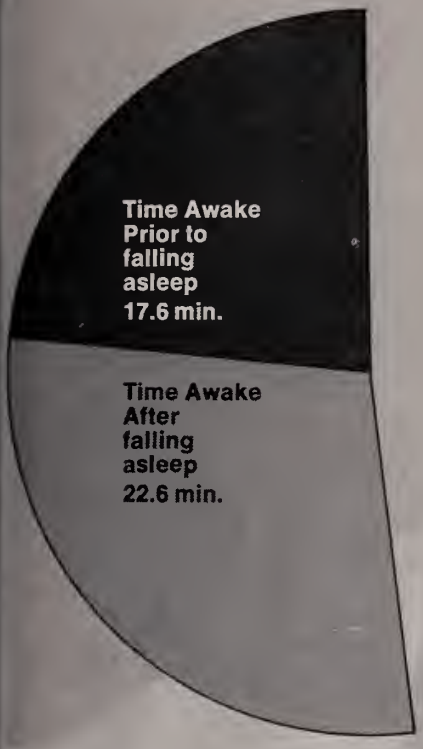
Before Dalmane (flurazepam HCl)



Measurements of sleep in the sleep laboratory are obtained with electroencephalographic, electro-oculographic and electromyographic recordings.

ınd slept through the night

On
Dalmane
(flurazepam HCl)



ıge sleep laboratory measurements in cited studies

neter	Before Dalmane	On Dalmane
required to fall asleep	33.6 min.	17.6 min.
time after onset of sleep	48.7 min.	22.6 min.
ber of wakeful periods after set of sleep	12.2	8.4
sleep time	420.0 min.	447.5 min.
sleep percent	88.6	94.5

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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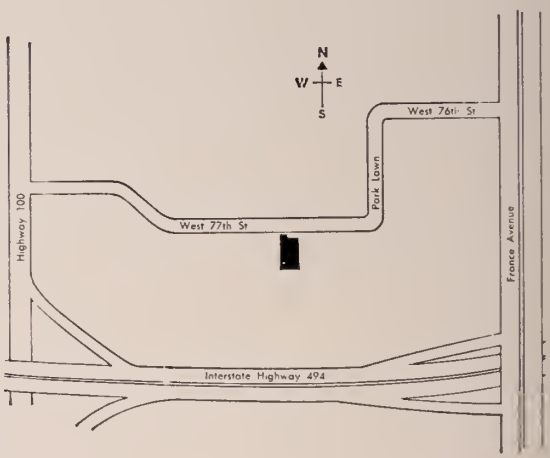
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President's Letter

National Health Care Policy

WITH 1971 FADING into the past, I think it is appropriate that I discuss National Health Care Policy. Much has been said regarding the health care crisis of our nation. Some people say that we have no system of health care; others, that our health care system is very adequate. I feel the health care in our nation is good. However, there are many things that need improving.

First of all, we must work to improve methods of financing medical care. We must develop a health care delivery system which addresses itself to catastrophic illness. Very few people, regardless of their income, can afford a long, lingering, complicated illness in their family. Everyone in the nation should be encouraged and assisted in having catastrophic illness coverage. We must seek a plan that the nation can afford. I do not feel it is right for the wealthy to become a burden on the taxpayer. The income tax credit system, which is recommended in the American Medical Association's Medi-Credit Proposal, in my opinion, is an excellent method of financing a health care system.

In the case of those who pay no income tax, the government would finance their total health care coverage. As the individual's income tax increased, the tax credit allowed by the government toward the purchase of health care coverage would decrease. Consequently, the medically indigent would have complete coverage financed by the government, and those who could afford to pay for their own medical coverage would be allowed to do so.

This health care coverage would be administered by the private insurance companies, which would be required to provide certain coverage, including that of outpatient services and preventive care such as immunizations and one physical a year. This health care plan should be set up so that a variety of health care delivery systems could function in any given area, thus permitting the most efficient systems to be developed in various geographic areas.

Besides the financing and the type of health care system, we must also address ourselves to the availability of health care. In the last five years there has been a 50% increase of students entering our medical schools. I become a bit impatient with people who continue to criticize the American Medical Association and our State organizations for holding down the number of graduates of our medical schools. This is absolutely not true! We are doing everything in our power to encourage State Legislatures and the Federal Government to fund expansion of our medical schools. However, in increasing the number of our medical students, we must also insist that the quality of their education be continued on a high level. This will require a greater sacrifice on the part of the medical school faculty. The private practicing physician also must now recognize the need to provide educational opportunities to medical students.

In Minnesota we have done several things which should achieve these goals.

1. We have increased our enrollment from 165 to 227 at our main campus.
2. In the fall of 1972, 24 students will be entering a new medical school at the University of Minnesota at Duluth and 40 medical students will be entering a new medical school at Rochester.
3. The State Medical Association and community physicians are providing learning opportunities to medical students under the Rural Medical Scholarship Program as well as Preceptorship Programs. The Minnesota State Legislature has also been very cooperative in funding part of this program.

With increased emphasis on the encouragement of primary health care in our medical

(Continued to page 1044).



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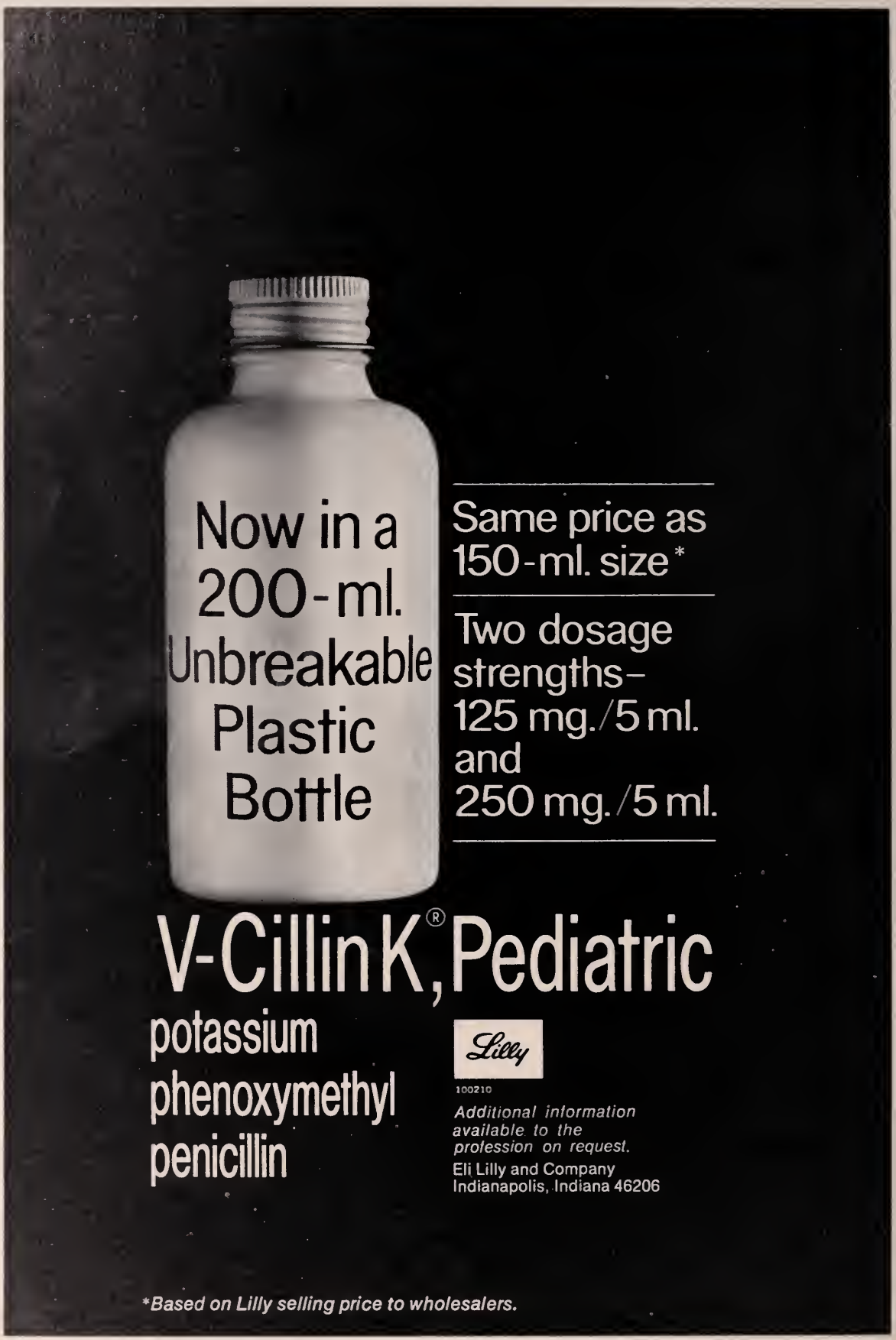
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Sudeck's Osteodystrophy

Its Pathogenesis, Prophylaxis, and Therapy*

K. LENGGENHAGER, M.D.*

ACUTE SUDECK'S OSTEODYSTROPHY is characterized by numerous, small, round "holes" which represent localized areas of bone resorption in the juxta-articular spongiosa, giving it a mottled appearance. Rieder[7] has shown that these holes are lined with osteoclasts, and our own studies confirm this (Figures 1 and 2).

Sudeck's osteodystrophy is a post-traumatic condition. Prolonged immobilization following trauma results in a partial capsular ankylosis of the adjacent joint. We believe that the subsequent attempts at loosening these adhesions cause an aseptic inflammatory reaction around the partially stiffened joint. Any benefit derived from the daily timid trials at active use and exercise is nullified by the reactive inflammation during the night. Clinically there is severe pain, and the affected area is acutely inflamed, hyperemic, and swollen. This inflammation spreads to the underlying bone and produces a collateral inflammation there. It may take weeks or even months for the inflammation and irritation to regress. Only then does the pain cease and the bone return to normal.



Fig. 1—Exostosis: Osteodystrophy in a 19-year-old man.

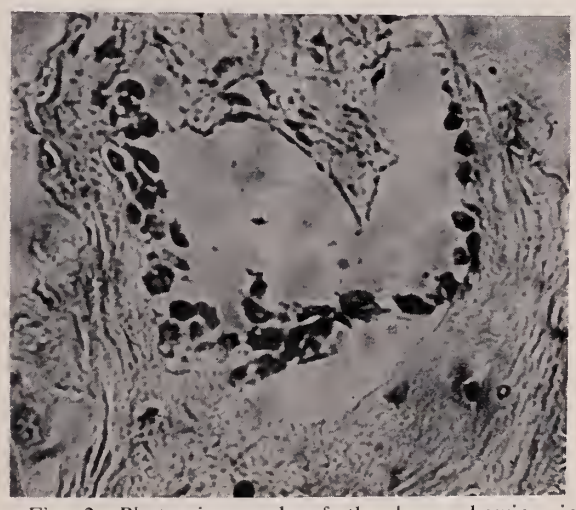


Fig. 2—Photomicrograph of the bone showing in Figure 1: Osteoclasts lining the resorption holes.

Pathogenesis

The pathogenesis of Sudeck's osteodystrophy has been difficult to explain. Modern German authors tend to incriminate a central nervous dysfunction.[1,2] In the American literature, no satisfactory explanation has been offered.[5] In the author's opinion, the theory of central nervous dysfunction is contradictory to the fact that Sudeck's osteodystrophy has not been observed in children, although many have an unstable vegetative nervous system, as evidenced by their predilection to episodes of vomiting, high fever, and tachycardia. The reason for this is that the injured extremities of children practically never develop capsular adhesions. They are thus spared

*Surgical Clinic University of Berne School of Medicine.

the remobilization process, along with the pain and the periarticular and osseous inflammation.

Rejection of Central Disfunction

The author would like to cite the case of a fisherman, apparently with a *perfectly stable nervous system,* who acquired a long-lasting, localized, parapatellar pain from a fall on the knee, with subsequent capsular ankylosis. After a few weeks there was evidence of Sudeck's osteodystrophy involving the patella and the femoral condyles (Figure 3).



Fig. 3—Sudeck's osteodystrophy in a fisherman.

The beef rib shown in Figure 4 was found in my dinner when I ate in an Alpine restaurant. It was full of small "Sudeck's holes." The traditional *tranquility of cows* rather speaks against a neurovegetative dysfunction. I would postulate a rib fracture as the possible cause of this osteodystrophy.

Finally, I found "Sudeck's stones" in the sea which had been gnawed upon from without by living organisms, but were composed of entirely *healthy limestone within* (Figure 5). Certainly no nervous system could be implicated in this case!

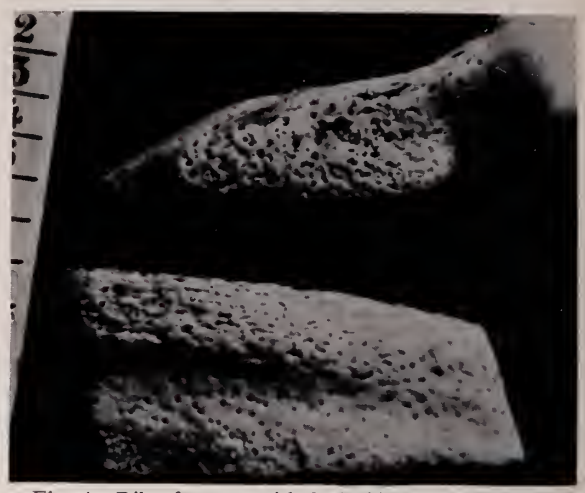


Fig. 4—Rib of a cow with Sudeck's dystrophy.

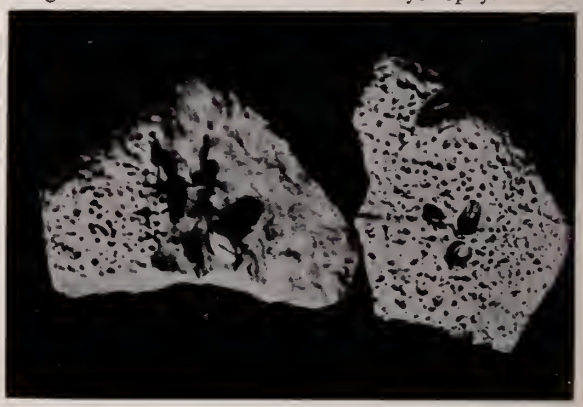


Fig. 5—"Sudeck-stones" in the sea.

Aseptic Inflammation

The author believes that the very painful remobilization process associated with capsular ankylosis leads to a prolonged periarticular inflammatory reaction which spreads to the underlying bone by way of the collaterals, and it is this inflammation that is responsible for the acute osteodystrophy.

What is the effect of an acute, aseptic inflammation? If 0.1 ml. of histamin in 1:50 dilution is injected intradermally, a white vesicle soon develops. The vesicle is white because fluid exudes from the arteriolar precapillaries with a pressure higher than that of the capillaries, thereby causing vasocompression in this area. With opening of the arteriovenus precapillary anastomoses, the vesicle soon reddens, and there is local hyperthermia. In this sterile, inflammatory, hyperthermic, acid environment, the osteoclasts begin to proliferate.

Why then are round holes formed by osteoclastic proliferation in the spongy bone although it has cuboid chambers? My explanation is that in the corners of these cuboid chambers the acid

of the osteoclasts is fighting a war on two fronts and that its activity is thereby diluted. For the same reason, a cuboid hole cut into limestone and filled with hydrochloride acid will become round (Figure 6). When this inflammatory process finally heals, the edema disappears, and with it the osteoclasts. Osteogenesis then begins rapidly.

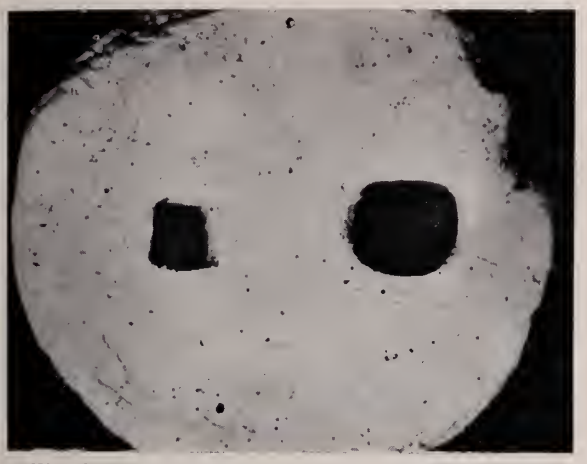


Fig. 6—The cuboid hole on the right side of the limestone becomes round after filling with hydrochloride acid.

Contrary to this sterile inflammatory process in Sudeck's osteodystrophy, acute osteomyelitis never produces this mottled dystrophy, because all the cells within the bone, including the osteoclasts, are destroyed by the toxins of the pyogenic micro-organism, resulting in large sequestra which are gnawed upon secondarily from the outside after the evacuation of the pus.

Neither is the mottling in Sudeck's osteodystrophy seen in cases with chronic, *cold* edemas of renal, cardiac or tuberculous origin. Tuberculosis produces localized destruction of the bone.

Prophylaxis

The shorter the post-traumatic immobilization, the less chance there is for capsular adhesions. This accounts for the fact that Sudeck's osteodystrophy is very seldom encountered after a stable bone union. The daily passive exercise of finger and toe joints are of great benefit to patients with a plaster of Paris cast. It prevents the later wearisome and difficult loosening and the prolonged inflammatory condition associated with it.

Therapy

Contrary to the current practice of treating such joints with gentle care, the above explanation demonstrates the necessity for shortening the painful period of remobilization.

Mobilization Under Anesthesia

According to my 25 years' experience: when regular physiotherapy fails to achieve considerable progress each week, mobilization of the partially stiffened joint under anesthesia is indicated. Generally one can hear and feel the dull, tearing sound of the adhesive capsular folds which have reverted to a normal degree of motility.

Splint and Exercise

The mobilized joint is fixed by a splint in the new position of flexion or extension. There should be careful, daily passive, and later active, slow exercises to the full extent of the newly-won excursion. Normal and painless mobility is attained quickly in approximately two to three weeks. Analgesics must be given during the first three days, just as they are following major operations. After three to four days the patient can already perform active exercises for two to four hours. The time and the number of exercises may soon be increased. The newly won joint positions, however, must be maintained during the night until any tendency for stiffness has disappeared.

I would also like to explain why a sympathetic block has a rather favorable effect on Sudeck's osteodystrophy: The former causes a pure hyperemia and no edema, in contrast to the later process which is a combination of edema and inflammation. The capsular adhesion, however, is not primarily influenced by the block.

Case Reports

Case 1.

A 62-year-old man suffered a distorsion of the knee which led to a painful partial stiffening. He had waited



Fig. 7(A) Case 1.—Sudeck's osteodystrophy before treatment.

in vain for the recovery of his badly stiffened joint for two years, when severe night pains forced him to enter the hospital. Figure 7(A) shows the mottled dystrophy of this joint before mobilization under anesthesia. The improved x-ray appearance seven weeks later is shown in Figure 7(B). There was normal and painless motility.



Fig. 7(B) Case 1.—Seven weeks after treatment.

Case 2.

Sudeck's osteodystrophy of the right hand developed in a 30-year-old woman with an injury caused by a wooden splinter five months previously, with one month's suppuration. Physiotherapy to remobilize the severly stiffened hand and finger joints was fruitless. The patient was thought to be a hysteric because of her complaints of recurrent pain. Figure 8 (left) shows typical mottled osteodystrophy. Mobilization was performed under anesthesia, followed by fixation in the newly-won flexed position by means of a removable plaster of Paris splint (Figure 9). She was hospitalized for 18 days. The control roentgenogram seven weeks after mobilization shows normal bone structure (with normal function of the hand and fingers) (Figure 8 (right).



Fig. 9 Case 2—Removable splint.



Fig. 8 Case 2.—(Left) Sudeck's osteodystrophy before treatment. (Right) Seven weeks after treatment.

Case 3.

After fracture of the radius four months previously this 60-year-old woman had increasing edema of the stiffened, paw-like right hand (Figure 10(A). Figure 10(B) shows Sudeck's osteodystrophy. We mobilized her wrist and all the finger joints and applied a removable plaster of Paris splint with the joints in the newly-won flexed position. Daily passive, later active exercises resulted in almost normal motility of the hand and fingers within seven weeks (Figure 11).

These were only three of our 50 cases of Sudeck's osteodystrophy successfully treated with the above method.

Summary

The role of a central nervous dysfunction in the pathogenesis of acute Sudeck's mottled osteodystrophy is rejected. Instead, an acute, prolonged, aseptic inflammation around the involved joint is postulated as its direct cause. The inflammation is secondary to the painful attempts at loosening the capsular adhesions of the stiffened joints after long immobilization. The osteoclasts grow specifically in the warm, acid background of inflammation and are responsible for the round holes of bone resorption. The inflammatory process can be reversed clinically in approximately two weeks, and roentgenologically in six to eight weeks, by means of forced mobilization of the



Fig. 10(A) Case 3—Acute "Sudeck's hand" in a 60-year-old woman.



Fig. 10(B) Case 3—Roentgenogram of the hand.



Fig. 11 Case 3—Seven weeks after treatment.

partially stiffened joint under anesthesia, followed by daily exercises. The effectiveness of this therapy was illustrated by three cases.

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Cover Photo

Mout Kilimanjaro

Dr. Robert E. Kasper took the photograph of Mount Kilimanjaro while he and his wife were touring the East African countries of Kenya, Tanganyika and Uganda. The picture was snapped in Northeastern Tanganyika. Kibo, the highest peak, stands 19,565 feet and is the highest point in Africa.

A Retina Reflax III camera with a 135 mm telephoto lens and Kodachrome II film was used by Dr. Kasper in taking this beautiful shot.

Dr. Kasper is a radiologist practicing in Minneapolis.

Our Thanks

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A Maverick?

Will a medical prophet soon appear to lead us out of the present infamy of the sick man being personally taxed for his medical care at the very moment he is least able to pay for it? Will a Prometheus bring us fire against the cold of medical neglect? He will appear, if he does, as a maverick. As of now we do not spy him. Just the same, remembering back over this life among the doctors, remembering how the mavericks of this chronicle have more and more of the devotion, the awe, of more and more millions of citizens, it seems to me that the times are building up for his coming.

*Paul De Kruif, Life Among the Doctors.

Bring Back the Mustard Plaster*

SEYMOUR HANDLER, M.D.†

IATROGENIC DISEASES and their appreciation are not new. Ben Jonson, a contemporary of Shakespeare, said in his play *Volpone:*

> Physicians are the greatest danger and worst disease to escape.

Voltaire (1694-1778), in addition to tormenting French royalty and laying the philosophical ground work of the French Revolution, had some choice commentary[1] about the physicians of that era:

> Doctors are men who prescribe medicine of which they know little to cure diseases of which they know less in human beings of which they know nothing.

Somewhat later, Arthur Young (1741-1820) clearly defined the limitations and potential harm of the medical care of his time:

> There is a great difference between a good physician and a bad one; yet very little between a good one and none at all.

Closer to our time, Oliver Wendell Holmes (1809-1894), the great American writer and physician teacher,[2] reacted sharply to the proliferation of worthless medicine of his day:

> Throw out opium . . . . throw out a few specifics which our art did not discover . . . . throw out wine . . . . and I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes.

Through these early periods, discerning observers realized that physicians did more harm than good, and the better medical circles adopted therapeutic nihilism. The age of therapy was reborn with Paul Ehrlich (1854-1915), who introduced salvarsan-"606"-for syphilis in 1910. Ehrlich believed that his "magic bullet" for syphilis was the first of many remedies that would strike the pathogenic agents of disease and spare the host. This utopian view of therapeutics has been discarded, because every medicine must affect the host in various ways in addition to the disease agent.

So we have passed from the therapeutic nihilism of Oliver Wendell Holmes to the therapeutic exuberance of our day. Society is daily bombarded in the news media with the advances of medical science—new drugs, therapies, cures for cancer just around the corner, etc. When the passage of time sheds light on the limitations of each new "miracle," the news media are unfortunately silent; debunking a "miracle drug" is not as newsworthy. The public's expectation of instant cures for all illnesses is the great paradox of medical care—the hope of instant good health and our gross inability to provide it.

Iatrogenic Disease

Iatrogenic disease is increasing at a rate proportional to the growth and complexity of medical care. Most iatrogenic diseases are *not* due to carelessness or ineptitude, but rather to a lack of appreciation of how much harm can occur through our well-intentioned efforts. If iatrogenic disease cannot be controlled, perhaps we should "bring back the mustard plaster!"

Drug Therapy

The thalidomide disaster of the early 1960s, causing major deformities in thousands of unborn infants, was the bomb that attracted the public's attention to the problem. Increasingly, physicians are made aware of adverse drug reactions by the Food and Drug Administration and the pharmaceutical companies. Studies in institutions[4,5] indicate that 10-30 percent of hospitalized patients have complications of drug therapy that prolong hospitalization. A recent study[6] of 6,000 medical

*Presented at the Annual Meeting of the Northwest Medical Association, February, 1971.

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†Associate Pathologist, North Memorial Hospital, Minneapolis.

patients indicates a fatality rate of 0.44 percent directly related to adverse drug effects. Common adverse drug reactions include hypokalemia due to thiazides, antibiotic gastrointestinal reactions, steroid-induced bleeding peptic ulcers, chloramphenical bone marrow depression and others. Current study[7] on oral hypoglycemic agents strongly suggests increased vascular disease and decreased longevity in treated patients. One wonders if the patient is better off with a little more glycosuria and a lot less atherosclerotic disease.

Among the most interesting adverse effects of drugs is the group of hitherto unknown diseases directly attributable to modern medicines. A partial list is outlined in the following Table.

TABLE

Drug	Disease
enteric coated KCl	small intestine stenotic ulcers
methysergide	retroperitoneal fibrosis
warfarin	intramural intestinal hemorrhage
tetracycline	pediatric tooth discoloration
nitrofurantoin	pulmonary infiltrates
long-acting sulfonamides	Stevens-Johnson syndrome
hydralizine, procainamide	lupus erythematosus

The 19th century observer, Peter Latham (1789-1875), clearly understood the basis of these new disorders:

> Poisons and medicine are often times the same substance given with different intent.

We are a pill-taking society.[5] The average physician prescribes some drug for 75 percent of his patients. Rather than spend the time to explain the natural course of self-limited disease and to reassure the patient, the busy physician "cops out" with his prescription pad. The lay public prefers action to light.

Exuberant Therapy

Polypharmacy

Doctor-shopping patients, over the years, accumulate a veritable drugstore collection in their medicine chests. The therapeutically exuberant physician fills up the medication sheet in the patient's chart, responding to each new complaint with another pill. Group practice or multiple consultants compound polypharmacy, where inadequate physician communication tends to more ordering of new medicines and less discontinuing of old ones.

Confusion and Toxicity

The older patient is less able to combat the onslaught of polypharmacy.[8] Multiple drugs are adversely effective, as one drug may inhibit or potentiate another. The unhappy result is a deteriorating, toxic and confused elderly patient, a baffling situation to the attending physician. After the bright consultant stops all medications, very often the patient dramatically improves: begins to eat, ambulate and cerebrate once again. If that desired result is not attained, at least the consultant is able to distinguish between the patient's basic illness and the confusing signs and symptoms related to polypharmacy.

Inadequate Diagnosis

Inherent in the polypharmacy of therapeutic exuberance is lack of a diagnosis and basic understanding of the clinical problem. When a patient is given 15 to 20 medications a day, frequently included are two or three antibiotics to "cover" the situation, although real evidence of an infection is not available. That patient will often receive more than one tranquilizer; and when he becomes lethargic, a psychic energizer is added. Sodium retention of steroid therapy is counteracted with diuretics, further compounding potassium losses. Treatment for mild normochromic anemia is the "shotgun" variety. The patient receives almost every diagnostic radiographic procedure available—all without a specific entity in mind—and he suffers from the inherent cost, discomfort and risk. What is behind all this well-intentioned but ill-conceived therapeutic exuberance? The answer may be only a psychological guess, but frequently the therapeutically-exuberant physician is compulsive and insecure, constantly currying favor with the patient and family by his "busywork," at the expense of a reasoned approach to patient care.

Nondisease

Nondisease has been described by Meador[9] as a particularly pernicious disorder of medical progress. The basic problem in nondisease is an inability to define the normal. A classic example of nondisease is illustrated in a study[10] of 93 school children in Seattle with a diagnosis of acquired or congenital heart disease. Complete cardiac evaluation revealed that only 19 percent had any heart disease. Of the 75 children with no cardiac abnormality, 30 were on restricted activity. One can only speculate about the life-long psychological and social problems of children labeled with cardiac nondisease.

Although the frequently discussed nondisease clinical entities are functional murmurs or normal epiphyses treated as fractures, laboratory parameters may be a larger problem. Normal laboratory values vary with age, sex, time of day, posture,

between laboratories, technical variation pre- and post-prandial and within the individual from time to time. A normal two-year-old with a 10-gram hemoglobin may be erroneously labeled as anemic, or a man with a serum uric acid of seven considered gouty, only on the basis of the laboratory test. We must learn the variables that contribute to the normal range and, before embarking on a complex diagnostic and therapeutic program on the basis of one laboratory abnormality, that test might well be repeated.

Poor Judgment

The physician who uses poor judgment in a complex medical problem has frequently compromised the patient with his therapeutic exuberance and lack of consultation. The following example would have been avoided with minimal consultation.

A 60-year-old female had a left radical mastectomy for carcinoma with two axillary node metastases. Postoperative irradiation was given. Nine months later a fairly discrete left pulmonary density was detected on x-ray. Hoping to remove a solitary metastasis, the same surgeon explored the chest. The pulmonary process appeared less discrete at surgery, and because of disinclination to cut across a tumor, a frozen section was not obtained. A total left pneumonectomy was performed, and the specimen revealed only radiation pneumonitis. Postoperatively, the bronchial stump broke down, causing an unrelenting bronchopleural fistula, requiring a two-stage thoracoplasty.

At several stages in the progress of this case, the exuberance and poor judgment of the surgeon could have been mitigated by consultation. The thoracotomy could have been prevented or, if the surgeon could not be restrained in his zeal to wipe out cancer with his knife, a frozen section could have prevented the pneumonectomy and subsequent complications. The name of the game is—"Get Help."

Diseases Due to Diagnostic Procedures

The modern physician, educated to make a diagnosis prior to instituting therapy, uses a vast array of diagnostic procedures—far beyond the harmless black bag of the house-call era.[11] Our diagnostic armamentarium, now extending to brain and myocardial biopsies, violates with impunity any area of the body. Far be it from me, as a pathologist, to talk against making a diagnosis. Posing as medical progress, our zeal in sticking needles, tubes, and other exploring instruments into any part of the body, adds to our diseases. The following case is illustrative:

In the evaluation of a presumed traumatic arteriovenous fistula in the neck, a young man had a Thorotrast carotid arteriogram. The contrast material was inadvertently injected into the carotid sheath (Figure 1), and the angiogram was not accomplished. Years later, the chronic tissue reaction (Figure 2) caused by the radioactive thorium compressed the carotid artery, necessitating a radical neck dissection.

The example illustrates the potential danger of any diagnostic procedure when the near and long-



Fig. 1—A-P X-ray of neck revealing Thorotrast contrast media extensively deposited in soft tissues of right carotid sheath.

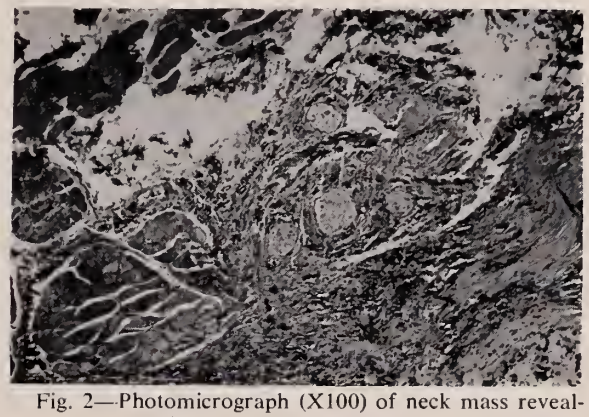


Fig. 2—Photomicrograph (X100) of neck mass revealing dense scar tissue enveloping muscle and nerves. Pigment is Thorotrast granules in macrophages and scar.

term hazards are not appreciated. Fortunately for this patient, intravascular injection of thorium dioxide was not accomplished, because he might now be suffering from a more serious complication of thorium—angiosarcoma of the liver.[12]

Diseases Related to Therapeutic Procedures

Transfusion

An 80-year-old female complained of mild dyspnea after climbing two flights of stairs to clean the attic. The hemoglobin was 3.8 grams, RBC 1 million, MCV 142, serum LDH 1800 WU, radioactive B_{12} absorption minimal and corrected to normal with intrinsic factor. Transfusion of two units of packed RBC resulted in pulmonary edema. Emergency measures, including venesection, prevented a fatality. She subsequently did well with parenteral B_{12} therapy.

The greatest risk to the newly-discovered pernicious anemia patient is physician panic when the low hemoglobin is reported. The patient may have carried the low hemoglobin for months, performing daily chores with only mild symptoms. Why then, should the physician panic and transfuse the patient, when vitamin B_{12} rapidly and completely causes a remission.

Oxygen

Oxygen toxicity is a recently recognized[13] hazard of well-intentioned therapy. Oxygen has achieved a place in medical care akin to God, motherhood and the flag. How often have physicians been called by the hospital about an emergency situation and the nurse suggests: "Doctor, should we start oxygen?" Unfortunately, this pure and almost virtuous gas can cause severe pulmonary damage if used in excessive concentration with certain types of inhalation equipment. In most situations, assisted respiration with room air is preferable to oxygen-enriched inhalation therapy.

Hospital Acquired.

Nosocomial infections[14] related to hospital therapy are not completely avoidable. Physicians should be aware that when certain things are done to patients in hospitals (operation, anesthesia, catheterization, etc.), the defense of the patient to the pathogenic organisms that abound is impaired, thereby setting the stage for the following infections: (1) postoperative pulmonary infections, (2) wound infections, (3) indwelling catheter urinary tract infections, (4) burn wound infections, (5) tracheostomy infections.

To be complete, a therapeutic or preventive-medicine disappointment may be added to our list: An intra-uterine device was inserted into a young female patient to control her family growth. After several months, menses ceased, her abdominal girth dramatically increased, and later, multiple movements were perceived from the abdomen. A flat film of the abdomen (Figure 3) indicated a twin pregnancy and the IUD. The breech baby returned the device to the obstetrician upon delivery.

Preventive Medicine

A 79-year-old widow, in excellent health, went to a physician at her daughter's urging for a "complete checkup." Routine proctoscopy detected a pedunculated sigmoid polyp. The polyp was snared and the base fulgurated. A few hours later she developed abdominal pain, emeses and fever. Laparotomy confirmed a sigmoid perforation at the fulguration site. The patient died of peritonitis a few days later.

This unhappy example explains the growing doubts[15] about the merits of preventive medicine in the asymptomatic patient, particularly senior citizens. Some observers believe that the patient who has achieved life into the eighth decade has demonstrated his heredity and durability, and that if he feels well and is asymptomatic, he is better off left alone. Many abnormalities or deviations



Fig. 3—Plain x-ray of abdomen revealing twin pregnancy at term and intra-uterine device.

from normal are unimportant to the patient's health and are better undiscovered and untreated. Much available therapy for asymptomatic conditions is meddlesome and may harm the patient. Increasingly, the merits of the annual physical are being questioned as having too little yield in treatable disease.[15] The annual physical may become a crutch for those who prefer unhealthy living habits, falsely believing that their annual visit to the doctor will keep them well. After discounting hereditary factors, the epidemic of atherosclerotic cardiovascular disease may be controlled by weight reduction, decreased dietary fat, avoidance of cigarettes, and regular active exercise. These are common-sense practices that should be nationally emphasized, not the futile fetish[15] of the annual physical.

The "Complete Workup"

The routine of performing a large battery of diagnostic tests and procedures that are not indicated by the patient's history and findings is expensive, tiring, dangerous and, most important, deters the physician from the straightest path to a diagnosis. Part of the "complete workup" etiology of iatrogenic disease is the fishnet practice of running all possible tests on the chance that the diagnosis might be made by luck. The practice is also popular with the physician seeking patient and family favor by appearing to do everything possible, leaving no stone unturned. What the patient really desires is a thorough and competent clinical evaluation and the fewest procedures necessary to confirm the clinical impression.

Referring a Medical Problem to a Surgeon

An elderly man, with 4+ proteinuria, BUN 62, urine specific gravity consistently about 1.012, and serum albumin 2.1 grams/dl, was referred to a urologist. Cystoscopy and retograde pyelograms under spinal anesthesia indicated a "mass" in a kidney. At renal exploration, the "mass" was found to be a simple cyst; kidney biopsy indicated endstage chronic glomerulonephritis. The patient expired soon after of renal failure.

The clinical problem was clearly diffuse and advanced medical renal disease. There is no way that a "mass" in one kidney can explain the patient's findings. Why, then, was this diffuse glomerular disease referred to a surgeon for evaluation? One answer, probably the most charitable, is that the referring physician did not recognize the nonsurgical nature of the disease. A more common reason, I fear, is that many physicians develop convenient and narrow referral practices, and that usually means a surgeon.

Surgeons have a real place in medical care, diagnostic as well as therapeutic. However, the surgeon is not the consultant for a medical problem. Though the training and thinking of a surgeon may lead to a surgical solution and, if the problem is not clearly either medical or surgical, the surgeon may prefer an operation. But the well trained and disciplined surgeon should know when *not* to operate as well as when operation is indicated. The problem is illustrated by the changing therapy of Hashimoto's thyroiditis which for years has been treated surgically but is now treated by the administration of thyroid hormone. Surgery is avoided except occasionally for diagnostic biopsy. However, in many communities, if this medical problem is referred to a surgeon, thyroidectomy will be performed.

The problem created by referring a medical condition to a surgeon is similar to seeking investment advice from a stockbroker. Generally the quality of the advice is purely a matter of luck. The only guarantee is that the investor will be persuaded to buy and sell stocks. The broker does his thing—persuade the investor to buy and sell. The surgeon does his thing—operate.

Psychosemantics

Our final disease of medical progress has been created by Robert Moser.[3] Psychosemantics covers a broad group of anxieties induced in patients by what physicians say or imply. The most severe examples occur in iatrogenic heart disease. Afflicted patients have other phobias and anxieties creating fertile conditions for a cardiac neurosis. However, the physician should not contribute to the problem. The mannerisms of the physician, facial expressions, prolonged auscultation—all serve to confirm to the anxious patient that his worst fears are realized. The physician must be clear and firm when the patient is told he has a normal heart; qualified statements are not in order. Some of the most insidious expressions[3] are:

"You have a good heart with a slight leak."
"Your heart is good, but take it easy."
"Take it easy and let me know if it gets worse."
"We can't find anything wrong with you, but check with me in a few weeks."

One can only speculate about the doubts and anxieties instilled in patients by such seemingly innocuous statements. Unfortunately, they may

serve as ample seed for an enduring and incapacitating cardiac neurosis.

Suggested Solutions

From this abbreviated outline of diseases of medical progress, the reader may develop a pessimistic attitude towards iatrogenic disease. The picture is not that bleak, but constant consideration of the possibility of iatrogenic disease is paramount. Suggested solutions are several.

Do Not Prescribe Unnecessary Drugs

Physicians should heed the announcements of the Food and Drug Administration, because their opinions represent the considered judgments of many experts and should not be interpreted as some nefarious government plot to regiment medical care.

Prescribe Less Medicine

Second, we should truly attempt to use less medicine. The major cause of preventable drug reactions is that too many pills are prescribed. Sir William Osler, the great Canadian physician, emphasized:

> One of the first duties of the physician is to educate the masses **not** to take medicine. Remember how much you do not know. Do not pour strange medicines into your patients.

Moser[3] gave this advice which could be broadened to include every diagnostic and therapeutic procedure:

> Do I know enough about this drug to prescribe it? Does the possible benefit to be derived outweigh the potential hazard?

Objective Evaluation

Third, the clinician should examine each new enthusiastically-introduced therapy with a level of cynicism approaching rejection. Significant advances stand unsupported in the cold light of objective evaluation. Countless new drugs, tests, operations, etc., are first described in lay magazines, press releases or by the drug detail man. Real contributions are calmly introduced in major medical journals with statistically controlled methods, inviting other investigators to prove or disprove the initial effort. Far too many physicians consider themselves completely capable of evaluating new drugs and therapies from their own experience. Great humility must be exercised to avoid being led down the garden path of one's own omnipotence. The evaluation of medical therapies requires the disinterested objective evaluation of large groups of patients, not the casual impressions gained from a few undocumented instances, where patient hopes and physician optimism distort the picture.

The surgical literature is replete with unproved and discarded therapies, reflecting the inherent enthusiasm of the surgeon's personality. Recall, over the past 10 to 20 years, gastric freezing[16] and the barrage of abandoned surgical procedures for ischemic heart disease. The same authors, who so enthusiastically abraded the pericardium[17] and ligated internal mammary arteries,[18,19] are now bypassing occluded coronaries with saphenous vein grafts. I don't know . . . . .

Handler's Dicta

I would suggest Handler's dicta, modestly put forth by the author after years of observation:

1. Is the parameter or sign observed in the patient normal for him?
2. What is the course of this condition unaltered by any therapy?

The above suggestions might be expected from a pathologist who is not subjected to the pressures and responsibilities of patient care. However, medical activity is frequently directed against patient situations that were normal for that patient. Further, the importance of knowing the natural course of a disease was earlier emphasized by Voltaire: "The efficient physician is the man who successfully amuses his patient while nature affects a cure."

The vast majority of illnesses are self-limited and disappear without or in spite of medical care. The medical quacks make good use of this fact. A small percentage of disease benefits from medical care, and another small percent does badly no matter what is done. Unfortunately, when the patient presents himself for care, the physician feels obliged to do something; that something could be harmful.

Conclusion

If the physician must do something—or the patient feels he must do something—consider a mustard plaster. The patient will know that something is being done. It will keep him busy while nature effects a cure.

Preparation of Ye Old Mustard Plaster[20]

1. Mix 2 tablespoons flour and 2 tablespoons dry mustard. Use less mustard for the pediatric patient.
2. Add enough cool water and stir to make a poultice.
3. Apply to clean, tattered old diaper and fold.
4. Apply to anterior chest until the patient screams: "I'm well. Stop already!"

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Presenting Medicus Schiller

"He was cramped into a uniform of the old Prussian cut, that on army surgeons had an even uglier, stiffer look; his little military hat barely covered his crown, behind which hung a long queue, while round his neck was screwed a horse-hair stock several times too small. More wondrous, however, was the nether part of him. Owing to the padding of his long, white gaiters, his legs seemed thicker at the calf than at the thigh. Moving stiffly about in these blacking-stained gaiters, with knees rigid and unbent, he reminded one irresistibly of a stork."*

The person so incarcerated in preposterous military uniform was no other than Regimental Surgeon Friedrich Schiller (1759-1805), Germany's illustrious poet, who, like John Keats, was only incidentally and temporarily a doctor during a long literary career.

Schiller was a product of Stuttgart's Karlschule, having been sponsored by Karl Eugen, the Duke of Wurtemberg, and enrolled in his military school to study law. Here the institutional routine was absolute: on order the students were commanded to rise, pray, eat ("fall to"), pray, study, eat, study, exercise, eat, study, retire.

(Continued to next page)

*Heinrich Duenster: The Life of Schiller.

Medicus Schiller

(Continued from page 979)

When Schiller was 16 the Karlschule expanded to include a department of medicine, to which Schiller, a "dullard" in law, volunteered to be transferred, and where he attended lectures, studied anatomy, and practiced on his fellow students. One "was afflicted with hypochondria, and Schiller was set to watch him. His analysis of the case is eminently sane. He finds it difficult to decide whether the young man's malady has its seat in the mind or in the bowels; whether too much brooding over hard problems has ruined his digestion and given him a headache, or whether a physical derangement has confused his ideas of duty and religion. He thinks there is a fair chance of curing the patient by means of medicine and good advice.—A youth who can talk thus of another's Weltschmerz is himself in no great danger from the malady."*

However, though he was conscientious, young Schiller's heart could never be confined to mundane duties; it was always taking off into the elysian fields of literature. He even contrived to get himself onto the sick list in order to be free to write poetry in bed; when "studying" he managed to hold Shakespeare or Plutarch concealed and hence undetected in the medical volume he was supposedly perusing.

At the end of his prescribed medical course, at the age of 21, he graduated creditably enough, having qualified for his final degree as Medicus by writing three essays: one monograph in Latin on the difference between two fevers and two monographs in German, both on the influence of the body and the soul or the interaction between the physical and the mental components of man. He was also the recipient of three prizes: in practical medicine, materia medica, and surgery.

One is inclined to suspect that his graduation was not so much the reward of drive and dedication but rather the result of his native German diligence and thoroughness. He had hoped that after termination of his course he might be released from army to private practice in order to have more freedom to pursue his literary bent. But the Duke said No!

So Schiller worked for 18 gulden ($7 or 8) a month as regimental surgeon to the Auge regiment of grenadiers: "consisting of some 240 time-expired men, who, in their patched scarlet uniforms and tall busbies, wandered about like so many meagre scarecrows."* He was also required to visit the hospital daily and appear regularly for parade. Which he dutifully did. But the whole bit was a blind alley to him! He wanted out! He showed no interest in training for promotion for eventual release; he invested in only one medical book, "Apothecary's Almanac," whereas his lean budget always seemed miraculously capable of sufficient expansion to purchase the works of classic literature.

Finally, when Schiller could endure his bondage no longer he fled. Away from his native province of Wurtemberg, beyond the jurisdiction of the Duke, and across the border into the Palatinate where, though a political fugitive, he could indulge his poetic genius to the utmost, leaving a literary legacy without which the world would be much the poorer.

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*Calvin Thomas: The Life and Works of Friedrich Schiller. Heinrich Duenster: The Life of Schiller.

Baker Tube Jejunostomy

Management of Small Bowel Obstruction

R. KENT MARKEE, M.D.* AND BENNETT E. UHLIG, M.D.*

Recurrent obstruction of the small bowel due to adhesions has plagued the general surgeon for many years. Removal of talc from the operating room, careful reperitonealization of the abdominal cavity, and more gentle handling of the abdominal viscera have helped to reduce the occurrence of these postoperative adhesions. These benefits, however, have been perhaps completely erased by the extension of intra-abdominal surgery to include the anterior, posterior, and total pelvic exenteration procedures. The frequent use of supravoltage therapy in the pre and postoperative treatment of advanced carcinoma, and the ability to salvage the massive intra-abdominal sepsis patient who, in the pre-antibiotic period had no chance for survival, have both contributed to the magnitude of this problem.

Every experienced abdominal surgeon is familiar with the extensive disruption of the serosal surface of the small bowel after an enterolysis procedure. If the abdomen is closed without an attempt to control the development of these adhesions to avoid sharp kinking of the bowel, mortality for this group of patients will be at least 15%.

The Noble Plication Procedure

In 1936 Dr. Thomas B. Noble[1-8] first described a procedure to provide "controlled" adhesions.

The Noble plication procedure provides that adjacent loops of small bowel be secured by continuous suture of catgut applied midway between the mesenteric and the anti-mesenteric margins of the bowel: a method widely applied for a period of approximately 20 years. However, it proved to have several disadvantages. The procedure was tedious and time-consuming: an important consideration for a critically-ill patient. Dr. Nat Wilson[10] reviewed a group of 113 patients operated under this technique and found that the incidence of postoperative fistula formation and obstruction was 8% for each of these complications. The operative mortality for the series was 5½%. He also demonstrated that the entire length of the small bowel had to be plicated, for, if such were not done, the plicated segment was prone to volvulus. Because of these complications and this significant mortality, enthusiasm for this operation waned rapidly after 1955.

Childs and Phillips Modification of the Noble Operation

In 1960 Childs and Phillips[9] presented a modification of the Noble operation. Using long needles and heavy silk sutures, the intestine was arranged in a plicated position and secured by means of three or four mattress sutures through the mesentery. It was soon apparent that the plicated arrangement of the bowel could not be maintained by trans-mesenteric sutures of catgut, but required non-absorbable sutures. These non-absorbable sutures, however, were found to serve as a nidus for postoperative abscesses and granulomatous lesions. Further, the obvious danger of injury to the mesenteric vessels and shortening and thickening of the mesentery made this procedure difficult, if not impractical.

Internal Splint for Fixation and Decompression

The first use of a long intestinal tube for an internal splint of the small bowel to control adhesions was suggested in 1955 by Dr. Raleigh White of Temple, Texas.[7] Dr. White's method was to pass a long tube, such as a Miller-Abbott tube or a Cantor tube preoperatively, and then, through an enterotomy incision with the tip of the tube in the small bowel, tie a vein stripper to it and advance the tube to the terminal ileum. The stripper was then removed through a distal enterotomy incision. The following year (1956) Dr.

*Portland, Oregon.

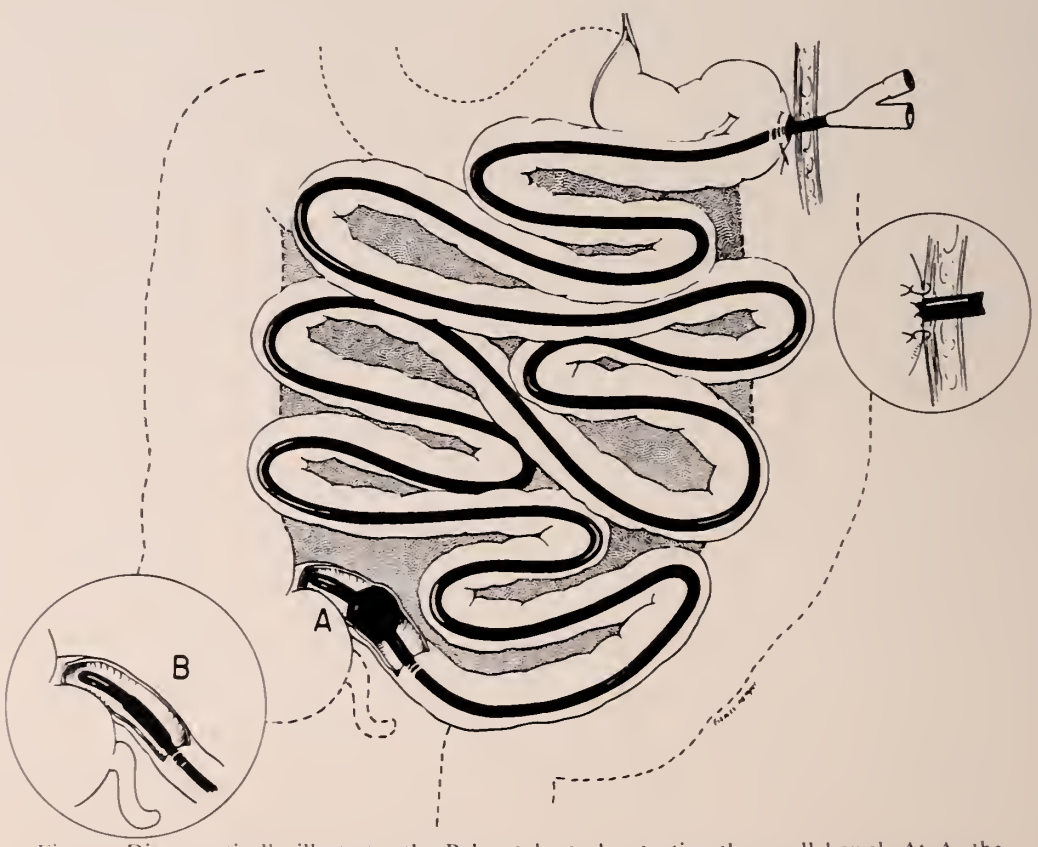
Joel Baker[4,6] designed a modification of the Bard-Foley urethral catheter for intra-operative surgical decompression of the distended small bowel. The first tube was 40 inches in length but has since been modified to a nine-foot length.[5] He used this tube to effect an internal splint for the stitchless plication of the small bowel. The advantage of the Baker tube is the palpable, inflated balloon which, by a milking manipulation, can be made to pass through the small bowel and be positioned in the terminal ileum. The balloon is then deflated. The apparent advantage of the long tube to effect the plication of the small bowel is that it can be done more rapidly than any of the procedures previously mentioned. The Baker tube can be used in chronic or acute obstruction, and also in the presence of generalized or localized intra-abdominal infection. It has been our observation from study of several Baker tubes injected with contrast material in the postoperative patient that the plicated position of the small bowel is actually not held, but the tube does effectively prevent sharp kinking of the small bowel.

The Baker Tube

The Baker tube is a pliable, plastic tube with a diameter of 5 mm. It is nine feet in length and the distal balloon can be inflated to a maximum diameter of one inch. The tip of the tube has two holes for suction, one inch beyond the balloon.

Description of the Procedure

The jejunum is identified approximately 10 to 12 inches from the ligament of Treitz. The Baker tube is then passed through a stab wound in the upper quadrant of the abdomen and, at the predetermined site in the proximal jejunum, an enterotomy incision is made. The tube is inserted and secured by placement of two pursestring sutures of catgut and then advanced with the balloon inflated through the small bowel as suction is applied to it for small bowel decompression. (Precautions: Advancement of the Baker tube should be done with some care. If the bowel is dilated and thin-walled, perforation of the bowel wall with the tip of the tube is possible. Also, as one is inserting the dilated balloon through the small



Figure—Diagramatically illustrates the Baker tube to be stenting the small bowel. At A, the balloon is shown inflated, and has facilitated threading the tube through the small bowel. Inset B illustrates the balloon deflated prior to closure of the abdomen. Inset at upper right shows the jejunum sutured securely to the anterior parietal peritoneum.

bowel, the diameter of the balloon may become greater than the diameter of the bowel, and a longitudinal, seromuscular tear may result.) After placement of the tube throughout the length of the small bowel, with the tip of the tube at the terminal ileum, the balloon is deflated. The jejunum is then sutured to the parietal perintoneum at the stab wound site of entrance of the tube with interrupted silk sutures (Figure). The tube can be attached postoperatively to low Gomco suction or simply left open for gravity drainage. It can be safely removed after two weeks or, if indicated, can be returned to the proximal jejunum and left in place for jejunostomy feedings.

Representative Cases

Case 1

A 29-year-old white male was admitted to Emanuel Hospital in December, 1970, with acute ulcerative colitis. Twelve days following total colectomy and ileostomy, the patient developed colicky abdominal pain and vomiting, and ceased to have ileostomy drainage. Abdominal x-rays indicated an upper small bowel obstruction. At operation the patient was found to have multiple intramesenteric abscesses and massive small bowel adhesions involving the entire jejunum and ileum. Following enterolysis, Baker tube jejunostomy was performed. The patient's postoperative course was complicated by a superficial wound infection, which required drainage and systemic antibiotics. On the twelfth postoperative day the Baker tube was removed and the patient was discharged on the sixteenth postoperative day, doing well.

Case 2.

A 47-year-old white male had a total cystectomy and bilateral uretero-ileal anatomosis for carcinoma of the bladder in May, 1970. Twelve days postoperatively there was evidence of a leak at the right uretero-ileal anastomosis. A collection of urine was drained from the right flank, and approximately two weeks later the patient developed clinical and radiological evidence of an acute small bowel obstruction. At operation, massive small bowel adhesions were found. Following enterolysis, Baker tube jejunostomy was performed. This patient's postoperative course was essentially uncomplicated. He was started on oral fluids on the sixth postoperative day. The Baker tube was removed on the tenth postoperative day, and he was subsequently discharged without further incident.

Case 3.

A 54-year-old white male had had a subtotal colectomy with ileoproctostomy for familial polyposis of the colon in 1950. Approximately one month postoperatively, this patient was operated on for acute small bowel obstruction secondary to a simple adhesive band. Polyps in the rectal segment were effectively controlled by fulguration every six months until January, 1970, when the rectal mucosa became active and several hundred polyps developed throughout all of the remaining colonic mucosa. Abdominoperineal resection with the construction of a permanent ileostomy was then necessary. Approximately three months after this operative procedure, the patient developed a small bowel obstruction secondary to massive adhesions requiring enterolysis and placement of the Baker tube. This patient's postoperative course was uncomplicated. He was started on oral fluids on the ninth postoperative day, the Baker tube was removed on the twelfth postoperative day, and he was subsequently discharged from the hospital.

Review of Cases (Table)

The collective experience of the surgeons at Emanuel Hospital, Portland, Oregon, for the period from January 1968 to January 1971, have been reviewed. All of these patients, because of the enterotomy performed, are contaminated cases; the superficial wound infection rate of 19% reflects this fact. It should be noted, however, that sepsis was present in 35% of this group of patients prior to operation, and that several required bowel resection. We have reviewed another series of 111 patients from our hospital who had some type of open bowel procedure on unprepared small bowel and have found that the wound infection rate in that series was 17.5%. For these reasons we feel that the Baker tube cannot be fairly incriminated as the cause of *all* the postoperative wound infections in this series.

TABLE
49 Patients Operated
January 1968 - January 1971

Baker Tube Jejunostomy	
Mean Age	52 years
Male	62%
Caucasian	90%
Primary Diagnosis	
Malignant Disease	45%
Acute Small Bowel Obstruction	20%
Intra-abdominal Sepsis	35%
Primary Indication for Use of Baker Tube	
Small Bowel Obstruction	67%
Prophylaxis	23%
Decompression	10%
Significant History	
Previous Irradiation	22%
Previous Small Bowel Obstruction	18%
Type of Jejunostomy Closure	
Stamm (purse-string)	70%
Witzel	30%
Postoperative Complications	
Wound Infection	19%
Recurrent Obstruction	4%
Fistula	2%
Total	25%
Operative Mortality	2%

Two of the patients with Baker tubes (4%) developed a recurrent bowel obstruction. In one of them the balloon was incompletely deflated and when distended was responsible for the development of an intussusception at the terminal

ileum. Re-operation was necessary. The second patient was an elderly female in whom the original obstruction was probably not completely relieved prior to placement of the Baker tube. This same patient developed a persistent fistula following removal of the Baker tube and died during the postoperative period. This was the only fatality relating to the procedure in this series (an approximate mortality rate of 2%). Sixteen (33%) of the entire group died as a result of their primary disease (massive sepsis or carcinoma).

Conclusions

The Baker tube jejunostomy for small bowel obstruction in this seriously ill group of patients was not the perfect procedure, as evidenced by the significant incidence of postoperative wound infections. It would, however, appear to be a step forward, inasmuch as it has been responsible for a significant improvement in the operative mortality. It should be emphasized that this procedure should not be applied to all cases of obstruction due to adhesions. It should be reserved for those patients with massive adhesions of the small bowel, and for those with recurrent small bowel obstruction. When exenteration procedures requiring sacrifice of wide areas of peritoneum and colectomy requiring sacrifice of the greater omentum are necessary, the prophylactic use of the Baker tube should be considered.

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A Rumbling was Heard from Maine to California

Samuel Brubaker Hartman—and who has not heard of his Peruna?—was born April 1, 1830, in Dauphin County, Pennsylvania. Hartman became a Bible salesman in Rural Ohio, got himself a medical education, and started in practice with a strong anti-drug bias. Later he became a bonesetter and advertised Peruna as a side line. Hartman believed in "gentle Stimulation" and Peruna had it, because of the 22 per cent of alcohol present. When the Treasury Department ruled that Peruna must have a detectable medical effect or be taxed as liquor, Hartman, then in his seventies, dumped quantities of blackthorn bark, a powerful cathartic, into the Peruna retorts. There followed a national rumbling of the bowels, especially in the more puritanical states, which abhorred the Whisky Trust. And in San Francisco there was some confusion as to whether the earthquake of 1906 was geophysical in origin or due to the new "improved" Peruna. There is a Peruna today, but a different product, recommended as a cough remedy, which meets all legal requirements. What about Hartman? Oh, yes, he was rated at about $2,250,000.*

*Gerald Carson: One for a Man, Two for a Horse: A Pictorial History, Grave and Comic, of Patent Medicines.

DERIVATIVELY SPEAKING

Physconia—from Greek *physkon* (pot-belly).

Hypertonic Parenteral Alimentation

in Infants and Children

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BERNARD J. SPENCER, M.D., FELIX A. McPARLAND, M.D., JOHN F. WALDRON, M.D.

INFANT MORTALITY IN a host of newborn gastrointestinal disturbances is often primarily related to the effects of starvation. In the past a method of parenterally delivering the nutrients necessary for healing with normal growth and development has repeatedly been sought; in general, such intravenous techniques have failed. In 1967, however, Dudrick and his associates in Philadelphia described a new technique which allowed prolonged hypertonic intravenous alimentation with resultant normal growth and development in puppies.[1] Since then, this method has been utilized successfully in adults, infants and children.[2,3,4,5]

Hypertonic parenteral alimentation consists essentially of the constant infusion of a hypertonic solution into the superior vena cava through a silastic catheter. The hypertonic solution contains 20% glucose with the amino acids and appropriate electrolytes and vitamins.

The amino acid solutions used in the infusate have been available and in clinical use for many years; the constant infusion pumps have been utilized frequently in varied clinical situations. Electrolytes and vitamins are given in ordinary amounts. Instead of the commonly used 5-10% glucose solution, the caloric requirements are met with a 15-20% solution. The administration of the infusate into the superior vena cava allows the rapid dilution of the hypertonic solution, thus minimizing its irritating effect on the vascular endothelium.

Clinical Material and Indications

During the past year on 11 occasions infants and children, unable to take enteric nourishment for a variety of reasons, were totally supported by parenteral nutrition for a period of from seven to 63 days. Ages ranged from the newborn to four years. Patients who have benefited from this technique include infants with in-utero ruptured omphalocele undergoing staged repair (Figure 1), gasroschisis, midget volvulus, small bowel atresias single and multiple, intractable idiopathic diarrhea, diaphragmatic hernia, meconium ileus, meconium peritonitis, entero-cutaneous fistulae, ileostomy in the newborn, complicated esophageal atresia with tracheo-esophageal fistula, severe burns, preoperative preparation for regional enteritis and ulcerative colitis and other gastrointestinal catastrophes (Table 1).

TABLE 1

Conditions in which hypertonic parenteral nutrition has been of value:

1. In-utero ruptured omphalocele
2. Gastroschisis
3. Small bowel atresias (single and multiple)
4. Midgut volvulus with loss of the midgut
5. Intractable idiopathic diarrhea of the infant
6. Diaphragmatic hernia
7. Meconium peritonitis
8. Entero cutaneous fistulas
9. Ileostomy in the newborn
10. Complicated esophageal atresia with tracheo-esophageal fistula
11. Severe burns
12. Preoperative preparation for regional enteritis and ulcerative colitis

Composition of Infusate

The infusate is prepared in the hospital pharmacy and is very similar to the one initially described by Wilmore and Dudrick and modified by Filler (Table 2).[3,9] It is prepared by the addition of 50% glucose to a 5% fibrin hydrolysate. The final solution of 20% glucose thus provides approximately 0.9 calories per milliliter. Appropriate electrolytes are then added to the solution, depending upon the individual situation of the patient. The potassium concentration is usually in the range of 30-35 mEq/liter and the sodium concentration, 35-40 mEq/liter. Other electrolytes added include magnesium sulfate and calcium gluconate. Multivitamins, vitamins B-12 and vitamin K are also added. Plasma is generally given twice weekly. Fatty plasma is given, par-

ticularly if prolonged intravenous therapy is anticipated; it provides essential fatty acids and trace elements (zinc, cobalt, manganese) which may not be included in the hypertonic infusate.

TABLE 2
Infusate Composition

Constituent	Amount (ml)
Fibrin hydrolysate (D. A.)	330*
Dextrose—50%	170
Calcium gluconate—10%	5
Magnesium sulfate—10%	0.5
Vitamin K-phytonadione 0.2 mg/ml	0.5
Vitamin B-12—10 mg/ml	0.3
Multivitamins—MVI	0.5†

*Abbott Laboratories, N. Chicago, Illinois
†U.S. Vitamin Pharmaceutical Corp., New York, N.Y.

Technique

Of significant importance is the proper placement of the silicone rubber cannula into the superior vena cava just above the right atrium (Figure 2). The catheter is inserted in the operating room under the usual sterile techniques using local anesthesia. A transverse incision is made over the right sternocleidomastoid muscle and, after isolation of the external jugular vein, the catheter is introduced and advanced to the level of the right atrium, its precise location being confirmed by x-ray study. The cannula is then brought out behind the right ear in a subcutaneous location utilizing a large-bore hollow needle to facilitate the passage of the catheter beneath the skin. Antibiotic ointment and a dressing are applied to



Figure 1(A)



Figure 1(B)



Figure 1(C)



Figure 1(D)

Fig. 1—(A) A newborn infant with an in-utero ruptured omphalocele illustrating the agglutination of stomach, small and large intestine. (B) In preparation for the staged repair, the viscera have been placed into a silastic container. During this time he received all nutrition parenterally. (C) Reduction of the omphalocele is nearly complete, twelve days after initiation of closure. (D) At one month of age, reduction is complete.

the exit point of the catheter after it has been secured in place with a silk suture, great care being taken to maintain the sterility of the exit site of the catheter. The dressing is changed every third day and an antiseptic and antibiotic ointment are applied to the exit site of the catheter and skin and a fresh dressing is applied.

The usual type of intravenous tubing is attached to the silicone rubber catheter. A milipore filter (0.22u) is included in the intravenous system to prevent any contamination which may have existed in the bottle of fluids from passing into the patient. A constant infusion pump, such as a Harvard or Holter Pump, is used to provide a slow, constant infusion of the hypertonic solution. The entire intravenous tubing is discarded every 24 hours. When the catheter is eventually removed, its tip is routinely sent for culture and sensitivities to evaluate possible contamination.

Clinical Management

A hypertonic solution of 15% glucose with the amino acid hydrolysate is generally the initial infusing solution, started at the rate of 100 ml. per kilogram per 24 hours. Within 24 hours the concentration is brought up to 20% glucose as the infant adjusts to the solution. Gradually, the rate is increased to 135-150 ml. per kilogram per 24 hours, as tolerated by the infant. In premature infants, it is often necessary to begin with a 5% glucose solution; and at times, because of their immature status, it is not possible to increase it to more than 10% glucose.

Great care must be taken during this period to observe the patient and to carry out laboratory and clinical determinations to avoid complications. Clinical determinations include the careful monitoring of vital signs, daily weights, and accurate urine outputs, with sugar analysis on each voided specimen. The determination of blood sugar and blood electrolytes is performed frequently during the first 24 hours and then daily for the next three days. Hematocrit determinations are also made. Potential hazards to be watched for include an osmotic diuresis from the large glucose load, and overhydration and congestive failure due to the large volume of fluids being administered.

In general, the blood sugars range from 70 to 129 mg/100 ml. It has been very common for the babies to spill one to three plus amounts of sugar in their urine. This quantity of glycosuria has been well tolerated and represents only about 1% of the administered glucose. Spilling four plus amounts of sugar in the urine often indicates significant hyperglycemia and may require a temporary decrease in the glucose concentration being administered. Infants generally have had less than one bowel movement per day while on hyperalimentation.

Complications

A number of complications can and do occur.[6,7] Sepsis is one of the more common. Candida albicans has been the most common organism encountered in our experience; others have

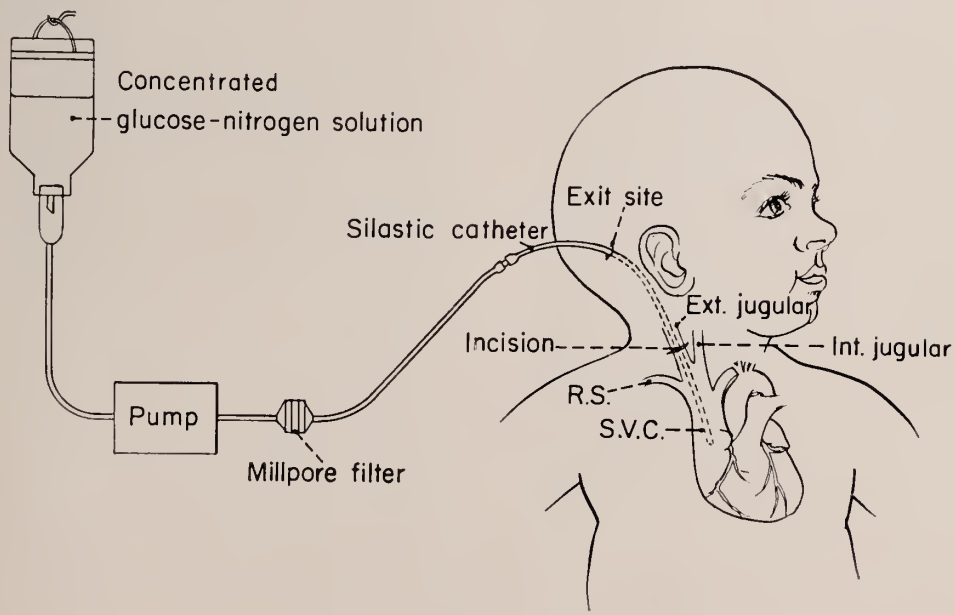


Fig. 2—Diagram of the delivery of the hypertonic infusate.

reported Staphylococcus aureus and Streptococcus fecalis. The presence of Candida in the blood stream usually does not require antimicrobial therapy but is managed simply by the removal of the catheter with rapid clinical improvement. The observation of daily temperature spikes or febrile episodes is a definite indication for catheter change unless there is some other obvious cause. The septic process is usually eradicated by simple removal of the catheter without the use of antibiotics. Another catheter may be inserted into another vein several days later, should the need arise.

Local skin infections and the extravasation of fluid as well as dislodgement and plugging of the catheter are also reported complications.[6]

One must remember that the infant may have severe hypoglycemia as the infusate is stopped at the end of a period of hypertonic parenteral alimentation. One must, therefore, gradually decrease the concentration of glucose being delivered and check blood sugars frequently during this period of the infusion.

Severe dehydration can occur, due to an osmotic diuresis; hence, constant vigilance is mandatory. The diuresis can be avoided by careful monitoring of the amount of glucose in the urine and blood. If the amount of sugar in the urine remains three plus or below, such a diuresis is unlikely.

Thrombosis of the superior vena cava was a frequent complication in the past when the firmer, more traumatic plastic catheters were used; however, with the silicone rubber catheters this is a very rare complication. Unfortunately, thromboses still occur and must be watched for.

Improper positioning of the catheter has been responsible, not only for complications but also for death in infants; hence, roentgenographic control of the placing of the intravenous catheter in the operating room at the time of the initial placement is an absolute necessity.[6,8]

Discussion

In those patients who have been unable to receive their nutritional requirements by the usual gastrointestinal route, hypertonic parenteral nutrition has been lifesaving. Our experiences reveal that infants and children receiving total nutritional support by hypertonic intravenous feedings have gained weight, healed wounds, grown and developed, and clinically benefited greatly from this form of nutrition. The duration of the infusion ranged from seven to 63 days. Weight gain is usually quite constant except in the severely depleted patient in whom an initial lag is often seen. If there is no weight gain while receiving the hypertonic infusion, the development of sepsis must be given strong consideration. The technique has allowed us to close ruptured omphaloceles in multiple stages more effectively because of the decompression of the gastrointestinal tract while maintaining adequate nutritional intake. Hypertonic parenteral nutrition has been of great value when dealing with a wide variety of gastrointestinal castastrophes, including enterocutaneous fistulae. By providing all nutrition intravenously the gastrointestinal tract is physically by-passed and put at rest; thus the chemical and physical stimuli for gastrointestinal secretions are decreased.[10] With positive nutritional balance enterocutaneous fistulae tend to heal spontaneously. Neonates with complicated anomalies such as esophageal atresia and diaphragmatic hernia have, in selected cases, derived benefit from this technique by having a constant, adequate supply of nutrients during their recovery phase.

A number of infants with an inadequate amount of absorptive surface area present in their gut or with faulty absorption have been helped by this technique. The small intestine, during this period of parenteral support, can compensate and adjust to a considerable extent.

While the complications must all be strongly kept in mind, hypertonic parenteral alimentation should be considered a highly useful and very important advance in the care of infants and children.

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3-9. May be secured from the author or the reprints.

Always behave like a duck—keep calm and unruffled on the surface but paddle like the devil underneath.

Pulmonary Reaction to Nitrofurantoin

HENRY T. SMITH, M.D.* AND ROBERT BERKSETH, M.D.*

THE PLEUROPNEUMONIC REACTION to Nitrofurantoin may be acute,[1,2] subacute,[3] or chronic.[4] The recent description of the diffuse interstitial pneumonitis or fibrosis associated with long-term use of the drug suggests that histologic and radiographic pulmonary changes may occur insidiously prior to the distressing pulmonary symptoms previously described. The following case report illustrates the occurrence of pulmonary signs in the absence of respiratory symptoms in a patient receiving this drug. Increased awareness of this form of presentation is imperative if we are to halt the presumed progression from such mild abnormality to chronic pulmonary disease.

Case Report

A 90-year-old white male was admitted to the hospital on May 19, 1970, for evaluation of fever and malaise of two days' duration. He had no other symptoms and specifically denied dyspnea, cough, chest pain, and orthopnea. He had had an internal urethrotomy and urethral dilation performed on the Urology Service three weeks prior to admission. His discharge medication at that time was Ampicillin 250 mg. q6h. One week before admission he was seen in the Urology Outpatient Department and his medication was changed to Nitrofurantoin (Macrodantin) 50 mg. q6h. One day before admission his temperature was 104°.

Significant physical findings at the time of admission were limited to a temperature of 100.2 and bilateral basilar inspiratory rales. The admission chest x-ray demonstrated "pulmonary vascular congestion" (Figure 1), whereas on the chest x-ray three weeks previously "the lung fields appeared clear." The leucocyte count was 12,000 with 78% neutrophils, 16% lymphocytes, and 6% eosinophils.

Because of the possibility of his illness being a reaction to Nitrofurantoin, the drug was discontinued. By the following morning he was asymptomatic. All radiographic signs of congestive heart failure cleared completely (Figure 2) over the succeeding five days without medications, dietary restrictions or limitation of activity.

Several articles[5,6,7,8] have reviewed the recent literature regarding pulmonary reactions to Nitrofurantoin. The most commonly described is that of acute dyspnea associated with chills and fever; this syndrome is most likely allergic in origin. The reaction may or may not develop with the first course of therapy. Symptoms may begin two hours to 10 days after the initial dose of the drug, or they may develop within hours after starting the second course. The interval is shorter with succeeding challenges with the drug. There may or may not be eosinophilia.

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Fig. 1—Admission chest x-ray on patient on 5-19-70 demonstrating pulmonary vascular congestion.

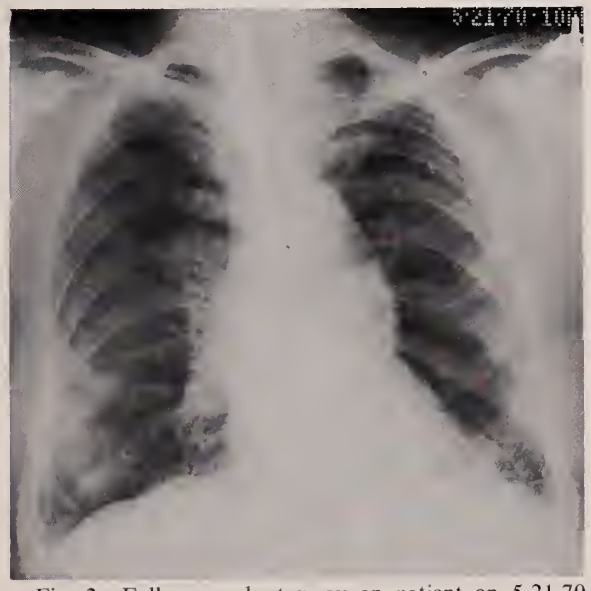


Fig. 2—Follow-up chest x-ray on patient on 5-21-70 demonstrating clearing of the "congestive heart failure."

Associated pleural effusions have been reported.[1] Pulmonary infiltrates are usually noted in both lower lobes. The acute presentation is commonly mistaken for pulmonary edema or pneumonia. The reaction is distinguished from pulmonary edema because of the absence of pink, frothy sputum; apical gallop; abnormal electrocardiogram, or a prolonged circulation time. It differs from bacterial pneumonitis by the absence of purulent sputum or predominant organisms in the sputum examination. Discontinuing the drug is usually the only therapy required.

The subacute[3] and chronic[4] reactions show no fever or eosinophilia. The patients usually complain of a persistent cough and increasing dyspnea. Chest x-rays show diffuse interstitial infiltration. Pulmonary function studies and arterial blood gas analysis demonstrate a restrictive ventilatory abnormality with impaired carbon monoxide diffusion, hypoxemia with mild hypercapnia. There is no decrease in air flow rate Asthma is not generally considered typical of the pulmonary reaction and has been reported only in patients with a history of recurrent asthma.[5]

No fatalities have been reported; therefore histologic examination is limited. However, in the chronic cases, lung biopsies have revealed chronic interstitial pneumonitis or fibrosis or both. The histologic appearance was not diagnostic, and was not unlike that seen in idiopathic, chronic, diffuse interstitial pneumonitis.

Therapy in these cases has consisted of discontinuing the Nitrofurantoin and using steroids, generally prednisone in doses of 20 mg. to 80 mg. qd. Partial to complete clearing of the respiratory signs and symptoms is usually noted during the next several weeks. The decision regarding tapering the steroid dose is based upon the patient's clinical response. The value of steroids has not been proved, but it is assumed that they may have a role in preventing irreversible pulmonary fibrosis.

The insidious nature of the process in the chronic presentation suggests a need for greater attention to routine chest x-ray, perhaps on a six-month basis, for patients receiving long-term therapy with Nitrofurantoin. Fever of undetermined origin, changes in respiratory symptoms, or changes in the chest x-ray necessitate a careful consideration of the possible role of the drug, whether it has been used on a short-term or a long-term basis.

Summary

A 90-year-old patient who had been treated with Nitrofurantoin for one week was hospitalized with fever, malaise, eosinophilia and a chest x-ray compatible with mild congestive heart failure. The drug was discontinued and the symptoms and signs rapidly subsided without additional therapy.

It is important to be aware of this problem so that we may avoid subjecting patients to therapy for conditions erroneously thought to be present, such as pneumonia, congestive heart failure and pulmonary emboli.

It is also imperative that we recognize the mild acute presentations of the pleuropneumonic reactions to Nitrofurantoin, since the unrecognized mild cases may progress to pulmonary fibrosis.

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War

They wrote in the old days that is is sweet and fitting to die for one's country. But in modern war there is nothing sweet nor fitting in your dying. You will die like a dog for no good reason.—Ernest Hemingway

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Let us endeavor so to live that when we come to die even the undertaker will be sorry.—Mark Twain

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Only a man's motives and mission make him great.—Forbes Epigrams

Intrapartum Mediastinal and Subcutaneous Emphysema

A Primigravida with Pre-Eclampsia

TAGHI EBRAHIMI, M.D.* AND KONALD A. PREM, M.D.*

THE SPONTANEOUS PASSAGE of air into the mediastinum and subcutaneous tissue of the upper anterior thorax, neck, head and retroperitoneum during labor is a relatively rare occurrence, and is often referred to as "Hamman's syndrome."[1,2,3,4] This complication is even less common in the earlier weeks of pregnancy and only a few cases have been reported in the literature.[5,6]

Subcutaneous emphysema at term was first described by Simonds of London in 1784.[7] Its occurrence, however, had been alluded to earlier by Louis Bourgeois, obstetrician to the Queen of France, of whom he stated, "I saw that she tried to stop crying out, and I implored her not to stop for fear her throat would swell."[1,3,8,9] The total number of such cases reported in the literature to date is estimated to be about 600.[1,3,11] The exact frequency of this complication is unknown. Kosmak[12] noted an incidence of one in 200 deliveries; Lam[9] reported one in 2,500, Spellacy and Prem,[1] one in 2,600, and Kubak and Abrams,[2] one in 100,000.

Case Report

A 20-year-old unwed primigravida was first seen in Seton Residence obstetrics clinic in January 1969. The initial physical examination showed a normal adult female with an initial blood pressure of 120/70 mHg. There was no history of chronic lung disease. She was seen regularly in prenatal clinic. At 38 weeks' gestation, the fetal size was estimated to be 3,500 to 3,600 grams. Because of a breech presentation, x-ray pelvimetry was obtained.

At 41 weeks' gestation, prenatal examination found two plus pitting pedal edema, a blood pressure of 148/89, one plus albuminuria, and an excessive weight gain. She was admitted to St. Joseph's Hospital for evaluation.

A 24-hour urinary estriol was normal. The edema disappeared with bed rest and diuretics. The patient was discharged in good condition after a few days.

At 42 weeks' gestation, labor began spontaneously. She was again admitted to St. Joseph's Hospital. The membranes ruptured spontaneously after admission. In spite of adequate sedation, her blood pressure during labor increased to 140/90, and a pre-eclampsia regimen was begun. Labor progressed rapidly. After a two-hour labor, she spontaneously delivered a male infant weighing 8 lbs. 9 ozs. under pudendal block and over a left mediolateral episiotomy. Although the one-minute Apgar was five, the infant did well.

During the second stage of labor, the bearing-down effort was extreme and her face became flushed and puffy. Following delivery, she complained of a tickling of the face, a swollen neck, a very stuffy nose, and an unusual noise (crepitation) when chewing. Because of the breathing difficulty and stuffy nose, neo-synephrine nose drops were ordered. Later the patient's mother became alarmed about the puffiness of her daughter's face, and the resident was called. On examination, the blood pressure was 120/80, and crepitation of the face, neck, and chest was detected. Sitting erect caused cervical pressure and increased the facial flush. A diagnosis of subcutaneous emphysema was made and confirmed by radiography (Figures 1, 2). Analgesics were prescribed. Gradually the dis-

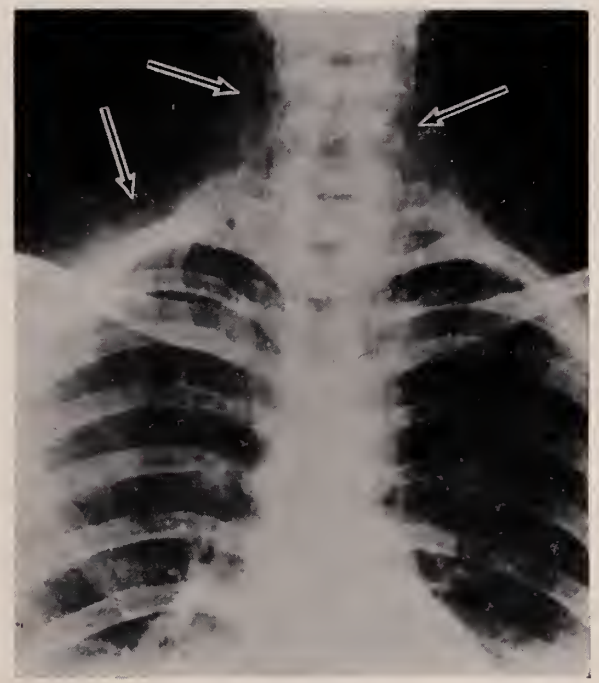


Figure 1

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comfort lessened and disappeared. A repeat radiograph several days later showed a complete absence of subcutaneous and mediastinal air. There were no abnormalities at her six weeks' post-partum check.

Discussion

Hamman[4] discussed mediastinal emphysema in 1945 before the American Medical Association in Chicago. He noted four pathways by which air may enter the mediastinum: (1) by way of the fascial planes of the neck; (2) through tracheal, esophageal or bronchial perforation; (3) from the retroperitoneal space; and (4) from interstitial tissue of the lungs. The last is the most common route, as air rarely enters the mediastinum through the first three.

The exact cause of Hamman's syndrome has never been proven, although several theories have been proposed. The most probable explanation is that under the violent strain of childbirth, or even the absence of strain, a rent occurs in the wall of a marginal pulmonary alveolus releasing air into the adventitia of a blood vessel, the lung parenchyma, and/or interstitial lung tissue. The escaping air can then follow one or more of the other routes previously mentioned.[13,14,15,16,17]

There are a variety of factors which may predispose the parturient to the development of mediastinal and subcutaneous emphysema. Some of these factors have been classified by Aisner and Franco[18] into the following groups operating singly or in combination: atelectasis with compensatory hyperinflation of adjacent alveoli as seen in upper respiratory infection, asthma, inhalation of foreign bodies and neoplasm of the lung; and increased intra-alveolar pressure resulting from forceful respiratory effects against pressure, such as in closure of the glottis, association with parturition, laryngospasm, playing wind instruments and tracheal insufflation secondary to resuscitation or positive pressure inhalation therapy.[18] Usually more than one factor is operating together with a certain intrinsic tissue deficiency or congenital deformity.[3,19,20] Mediastinal emphysema may occur spontaneously when at rest or during sleep, probably due to some inherent weakness of the alveoli.[4,9,13]



Figure 2

Although extremely rare, there are several congenital pulmonary or bronchial malformations that could manifest themselves by rupture and allow the escape of air into the mediastinum under the stress of labor or similar situations in which intra-abdominal pressure is increased by breath holding. The following anomalies might exist: (1) a supernumerary bronchus ending blindly as a tracheal diverticulum or a cyst, (2) an accessory lung originating from the tracheobronchial tree, (3) accessory lung tissue originating from the esophagus or a congenital weakness in the wall of an esophageal diverticulum, and (4) pathologically congenital bullae.[19,20]

As in the case reported, the symptoms of mediastinal and subcutaneous emphysema may not be observed until the post-partum period and may be ignored because of the observer's unfamiliarity with this condition. Most patients are young primigravidas. Although the nurse-attendant in this case noticed that the patient's face and neck appeared to be more swollen than usual and that she had a stuffy nose, she did not recognize the significance of these signs. With a history of pre-eclampsia and intra-partum blood pressure elevation, she was more concerned about the possibility of pre-eclampsia.

The diagnosis of subcutaneous emphysema should be entertained when a patient, after bearing down hard in the second stage of labor, complains of "crackling" sounds heard with movement of the jaw. Crepitation of the subcutaneous tissue of the face, neck and anterior thorax is diagnostic. Other

signs and symptoms frequently found are discoloration of the skin, dysphagia, and aphonia. The presence of air in the soft tissue may be confirmed by radiograph. This complication is usually accompanied by pneumothorax; but, as the air is forced into the subcutaneous tissue by bearing down during labor, there is no time to demonstrate pneumothorax. By the time of radiograph, the air has already escaped from the thorax.

Treatment is conservative and consists mainly of supportive measures. A chest radiograph rules out pneumothorax. It is important to distinguish this condition from pulmonary embolism, pericarditis, myocardial infarction, mediastinitis, dissecting aneurysm, and angina pectoris.[1,3,5,13] Symptomatic treatment with analgesics, sedation, and perhaps oxygen is recommended.[1,21] If increasing mediastinal pressure causes cardiac tamponade, mediastinotomy may be of great value.[1,2,5,14]

This condition seems to be most common in the young primigravida and clears rapidly with complete recovery, usually within two weeks.[1,3,5] According to the literature, subsequent labor rarely produces a repeat occurrence. Although the prognosis is excellent, two deaths have been reported.[19] Elective forceps delivery is recommended to prevent straining in the second stage of labor.[1,2,9,21] In the reported case, the diagnosis was delayed because of the similarity of the facial features of pre-eclampsia and subcutaneous emphysema.

Summary

Similarity of the appearance of the head and neck in subcutaneous emphysema and in pre-eclampsia may confuse the clinical pictures and cause a delay in the correct diagnosis.

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Danger

Fat folks should realize the extra strain on their heart by their additional blubber. Every five pounds of surplus weight means three miles of extra blood vessels must sprout to service that fat. And the more miles of "pipes", the greater must be the pressure in the central pumping station, the human heart!*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

An Account of the Foxglove*

by William Withering†

In the year 1775 my opinion was asked concerning a family receipt for the cure of dropsy. I was told that it had long been kept a secret by an old woman in Shropshire who had sometimes made cures after the more regular practitioners had failed. This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant with these subjects to perceive that the active herb could be no other than the Foxglove.

July 25th—Mrs. H. of A. near N. between forty and fifty years of age, a few weeks ago, after some previous indisposition, was attacked by a severe cold, shivering fit succeeded by fever: great pain in her left side, shortness of breath, perpetual cough, and after some days copious expectoration. On the 4th of June, Dr. Darwin was called to see her.

On the twenty-fifth of July I was desired to meet Dr. Darwin at the lady's house. I found her nearly in a state of suffocation, her pulse extremely weak and irregular, her breath very short and laborious, her countenance sunk, her arms of a leaden color, clammy and cold.

In this situation of things I knew of nothing likely to avail us . . . and accordingly I proposed that the Digitalis be tried; adding that I had sometimes found it to succeed when other, even the most judicious methods, had failed. Dr. Darwin very politely acceded immediately to my proposition, and as he had never seen it given, left the preparation and dose to my direction. We therefore prescribed as follows:

Rx. Fol. Digital, purp. recent oz. iv. coque ex Aq. fontan. purae lb iss ad lb i. et cola.

Rx. Decoct. Digital. oz. iss. Aq. Nuc. Moschat. oz. ii. M. fiat haust 2dis horis sumend.

The patient took five of these draughts, which made her very sick, and acted very powerfully upon the kidneys, for within the first twenty-four hours she made upwards of eight quarts of water. The sense of fulness and oppression across her stomach was greatly diminished, her breath was eased, her pulse became more full and regular, and the swelling of her legs subsided.

July 26th—Our patient being thus snatched from impending dissolution, Dr. Darwin proposed to give her a decoction of pareira brava, and guiacum shavings, with pills of myrrh and white vitriol: and, if costive, a pill with calomel and aloes.

July 30th—This day Dr. Darwin saw her, and directed a continuation of the medicines last prescribed.

August 1st—I found the patient perfectly free from every appearance of dropsy, her breath quite easy, her appetite much improved, but still very weak . . .

It was from this kind of experience that I ventured to assert, in the Botanical Arrangement published in the course of the following spring that the Digitalis "merited more attention than modern practice bestowed upon it."

Editors Note: I suppose we are going to be forced to listen to the currently popular plea for acupuncture lest we miss something from the ancient Chinese cultists.

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*Condensed and quoted from Berton Roueche: Curiosities of Medicine.

†William Withering (1741-1799) was a Birmingham, England, physician. He introduced digitalis (foxglove) in the pharmacopoeia.

Chronic Bromide Intoxication

ROBERT R. REICK, M.D.*

LOCOCK INTRODUCED bromides as anticonvulsants in 1857. For over 100 years now, they have also been used as sedatives. Today they are present in proprietary medications, such as Bromo-Seltzer, Bromo Quinine, and Miles Nervine. Despite the availability of these drugs, acute bromide poisoning seldom occurs because bromides irritate gastric mucosa when taken in large amounts as a single dose.[1] But because the half-life of bromide in the human is 12 days, it is possible to build up a toxic blood level through the daily use of such compounds.

Chronic bromide poisoning is surprisingly common. Ten percent of the patients admitted to a psychiatric hospital had serum bromide detected, and two percent had clinically significant bromism.[3] Physicians are often responsible, in part, for enabling bromide abuse to occur. In reviewing 27 cases of bromism from Boston City Hospital, Perkins found physicians had initially prescribed bromide-containing compounds in about 50% of the cases.[4]

The clinical picture presented by chronic bromism can be perplexing.

Case Report

A 53-year-old white woman, was brought to the hospital by friends because of confusion, diminished intellectual function, loss of memory, bizarre behavior, and visual and auditory hallucinations for six weeks. Four years before, the patient was hospitalized at a state mental institution because of an acute psychosis. But she recovered and had been working as a switchboard operator and functioning well. There was a history of chronic alcoholism, but no evidence of recent intake. On physical examination she was confused and disoriented; deep tendon reflexes were symmetrically hyperactive. A left Babinski toe sign disappeared within a few hours. Laboratory studies revealed the diagnosis of bromism, and this was confirmed by further history when the patient finally became able to communicate. Treatment with NaCl, 6.0 gm. daily, and furosemide, 80 mg. daily, was given.

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Symptoms of Bromism

Common symptoms of chronic bromide intoxication include mental confusion and disorientation, stupor, hallucinations, nervousness, headache, gait disturbances, irritability, and insomnia.[4,5] These signs and symptoms are due to bromide ion, not to incidental hypochloremia or to the cation with which it is ingested.[4] Symptoms are often aggravated by further ingestion of bromides by the patient to relieve his complaints. With the long half-life of bromide, this simply steadily increases the serum level of the toxic agent.

Physical Findings of Bromism

Physical findings include weakness (even to the point of hemiparesis), reflex changes which vary from day to day, brown furry tongue, memory loss, low-grade fever and, in about 10% of cases, skin rashes of variable type. Other diseases often cloud the diagnosis in persons who are using bromides. These diseases include nervous system disorders, generalized arteriosclerosis, heart disease, malnutrition, and other forms of drug abuse.[5]

Serum Bromide Levels

Measurment of serum bromide levels confirms the diagnosis. A level of 75 mg.% (9 meq/L) is grounds for suspicion in an individual with unexplained neurological findings, and a level of 150 mg.% (19 meq/L) is almost always associated with clinical disease.[1] Serum bromide levels do not correlate well with the extent of signs and symptoms. A clue to bromide intoxication is unexplained elevation of serum chloride, as measured by the autoanalyzer. This method is based on halide displacement of mercury from a mercuric-thiocyanate complex, resulting in the formation of ferric thiocyanate. Both chloride and bromide will displace mercury in this reaction.[6] In the case presented, the serum chloride was 137 meq/L when the serum bromide was 194 mg.%.

Bromide as An Ion

Bromide is primarily an extracellular ion, but a significant intracellular level exists in erythrocytes and neurons. The ion is found in all extracellular body fluids and secretions.[7] In experiments on rabbits, Pollay showed that the CSF/plasma ratio for bromide depends on the plasma level, but it always remains less than one. He further found that the brain/CSF and brain/plasma bromide ratios remained low, regardless of the blood levels of bromide. He hypothesized that this might be due either to oxidation of bromide by brain tissue or to the presence of a bromide pump.[8]

Bromide is eliminated from the body by the kidney, but at a slow rate. The kidney maintains body halide concentration at a normal level. Bromide ions are preferentially reabsorbed by the kidney in competition with chloride. The ratio of bromide to chloride reabsorbed is almost completely determined by the ratio of the two ions in the glomerular filtrate.[9]

Treatment of Bromism

To treat bromide intoxication you must increase the renal excretion of the ion. Administering sodium chloride or ammonium chloride in large doses competitively inhibits bromide reabsorption. By adding a mercurial diuretic to sodium chloride, Hussar and Holley increased urine bromide levels by 60%. Adding mercuhydrin to ammonium chloride brought an increase in renal bromide excretion of 130%.[10] Adamson *et al.* combined ethacrynic acid with mannitol to bring about a brisk diuresis. The half-life of bromide was changed from 12 days to 1.65 hours with this regimen. Urine bromide excretion was increased from 4% of the filtered load to 34% during the diuresis.[7]

Varying Bromide Levels

When the serum bromide level is rapidly lowered, a rebound phenomenon sometimes occurs. In a case report by Adamson the serum bromide level decreased from 280 mg.% to 10 mg.% in nine hours. However, five hours later the serum level had increased to 134 mg.%. The improvement in the patient's mental status persisted despite this rebound.

In the case reported here, the serum level went from 440 mg.% on the day definitive treatment was started down to 194 mg.%, then up to 329 mg.% over a five-day period. Despite this variation in serum levels, the patient improved daily and symptoms did not recur. Serum bromide levels probably vary during diuresis because bromide ions shift out of cerebrospinal fluid and intracellular compartments, though proof for this is lacking. These shifts apparently pose no danger to the patient. Though it is possible to lower the serum bromide level rapidly by the liberal use of diuretics, clinical improvement may not be quite so rapid. Full recovery of mental function may take four to 10 days or even longer, but prognosis for return to the pre-morbid state is good. Caution must be exercised, of course, not to create electrolyte imbalance through brisk diuresis.

Summary

A 53-year-old white woman, who for six weeks had become increasingly confused, had a serum bromide level of 550 mg.% Physicians treated her with oral sodium chloride and a diuretic, and she improved within 72 hours.

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Take Time TO WORK—It is the price of success.

Didactic-Clinical

Angiography of the Alimentary Tract*

MANUEL VIAMONTE, JR., M.D.†

ANGIOGRAPHY FOR THE evaluation of some gastrointestinal disorders includes arterial studies (aortography with selective and superselective arteriography), venography of the portal and caval circulations, and retroperitoneal lymphography. We limit our comments to selective arteriography.

Indications

1. Unexplained abdominal pain.
2. In acute or recurrent gastrointestinal bleeding of unknown cause, to establish the site and possible cause, and as part of the treatment of some patients bleeding massively into the gastrointestinal tract.
3. Gastrointestinal tumors.
4. Prior to certain radical operations (i.e., total colectomy and total pancreatectomy) in order to avoid vascular complications, which may follow inadvertent section of aberrant or supplementary arteries.
5. To confirm patency and hemodynamic results of surgically constructed shunts.
6. Following abdominal trauma in selected patients.
7. When a vascular lesion is suspected, such as aneurysm, angioma and arteriovenous fistula.

Contraindications

The percutaneous transfemoral approach is the technique of choice in most situations. However, in the presence of severe occlusive peripheral arterial disease: wide pulse pressure (such as in severe aortic insufficiency), hemorrhage diathesis, and severe arterial hypertension (diastolic pressure over 110 mm. Hg.), we use a left brachial approach following open arteriotomy. In the presence of peripheral occlusive disease, or when the vascular anatomy of the celiac or mesenteric trunk does not lend itself to superselective catheterization (failure from the femoral route), we catheterize the abdominal aorta via the axillary or brachial arteries.

Technique

The patient lies comfortably in a cradle‡ and is kept warm and hydrated before, during and after the angiographic examination. Minimal sedation and bowel preparation are standard pre-angiographic orders. The stomach is distended with a gas-containing soft drink when doing celiacomesenteric arteriography. A roentgenogram of the abdomen in the frontal projection is taken before and after the angiographic examination.

Guided Catheters

We use "guided catheters"# with a maximum outer diameter of 2.3 mm. (No. 7 French catheter) or smaller. These catheters have positive torque (rapid response of tip to rotation), a small open tip and two to four large side holes. To facilitate the introduction and advancement of the catheter we use a J-shaped-tipped, disposable, teflon-coated guide wire, a short arterial dilator, and plastic cannulas. Superselective catheterization may be facilitated by the use of deflector assemblies.§ Pre-shaped catheters may be utilized for superselective catheterization procedures. A double curved catheter with a semi-soft tip and a firm body is used for catheterization of the celiac and mesenteric trunks as well as for mid-stream aortography.

Under fluoroscopic guidance, using image intensification-television fluoroscopy, the catheter is manipulated into the selected vessel and a test injection is made at the same delivery rate as for the final injection. For example, for celiac trunk injections we use 40 ml to 60 ml at 10 ml per second. We inject 1 ml at the 10 ml per second delivery rate, and observe fluoroscopically the response of the catheter tip; if the tip recoils, we decrease the delivery rate. We employ the

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‡Angiographic cradle made by Hobbs Industries, Miami, Florida.

#Ducor catheters made by Cordis Corporation, Miami, Florida.

§Cordis Deflector and Muller-U.S.C.I. deflector systems. The latter is made by U.S.C.I. Co., Glenn Falls, New York.

fastest delivery rate that will not cause recoil of the catheter tip.

Contrast Material

Contrast material is injected with an automatic, flow-rate-controlled injector.*

We inject 30 ml to 50 ml into the superior mesenteric trunk and 15 ml to 30 ml into the inferior mesenteric artery. Diatrizoates of 75 or 76 percent concentration are used. For superselective catheterization, the usual volume per injection ranges between 10 ml and 20 ml; however, for superselective injection of the splenic artery we inject 40 ml to 100 ml, depending on splenic size. We record our study on a rapid film changer programmed at two per second for the first four seconds and at one per second for seven to 14 seconds, depending on the injection site and pathology.

Filming Factors

Optimum filming factors include the lowest possible KV (65-80) to provide optimum contrast, the highest MA (700-1000) and the shortest exposure time (less than 1/30 sec.). The radiographic tube should have a small focal spot (0.3 to 1.2 mm); and for magnification radiography, one must use a 10,000 rpm rotating anode x-ray tube with a focal spot size 0.3 mm or smaller. For magnification radiography the patient is usually placed equidistant between the x-ray tube and film changer, or closer to the former. This can be accomplished either by elevating the patient (we use a specially designed rotating elevating cradle for this purpose) or by lowering the film changer.

Pharmacoangiography may provide valuable information when we study *pancreatic lesions, gastrointestinal tumors, and the portal circulation.* We use epinephrine in doses of 20-25 micrograms when injected into the celiac trunk or 10-15 micrograms when injected directly into the hepatic artery. Epinephrine preferentially constricts the splenic arterial bed and also the normal vessels, while pathological vessels may remain undisturbed. Enhancement of *hepatic arteriography in liver neoplasias* may be observed following the injection of epinephrine. Tumor nodules may be best outlined in post-epinephrine angiograms.

Vasopressin infused slowly into the celiac or mesenteric trunks has been employed successfully as part of the treatment of acute gastrointestinal bleeding. The dose recommended is 0.1 unit per minute. Abdominal pain is a guide for the speed of the infusion. Bradykinin injected into the superior mesenteric artery provides the best degree of opacification of the portal vein when doing mesenteric-portography, as for example, in post-splenectomy patients suspected of having portal hypertension. We use Priscoline (20-40 mlgms.) injected into the SMA to enhance the venous phase.

*V-H Injector made by Barber-Coleman Co., Rockford, Illinois.

Complications

It is quite unusual to see hypersensitivity reactions. Nonetheless, the angiographer must be prepared and knowledgeable in the treatment of all types of medical emergencies. Complications can be minimized by selecting the most suitable route, avoiding prolonged examination, using minimal manipulation of the catheter, particularly in infants and in the older age group, and by careful observation of the patient during and following the procedure. To minimize complications at puncture site we suggest the use of the smallest catheter with a soft tip which allows delivery rates of up to 20 ml per second without catheter rupture or tip-recoil.

Indications for Angiography

Abdominal Angina

The syndrome of abdominal angina may be associated with decompensated obstruction (complete or incomplete) of larger or small arteries that supply the gastrointestinal organs. Celiac artery stenosis is to be considered hemodynamically significant when celiacomesenteric anastomotic vessels are demonstrated and when the area of stenosis involves at least two thirds of the lumen of the vessel. Surgery is advised when postprandial abdominal pain cannot be explained by any other abnormality, and after careful radiographic examination of the stomach, duodenum, bowel and biliary tract. Periceliac infiltration of Xylocaine is used to assess the pain problem.

Vascular Occlusion

Arteriosclerosis and embolism are frequently the cause of abdominal angina. The pain may be continuous or intermittent and usually appears in the immediate post-prandial period. Vomiting, diarrhea and weight loss may be present also. Lateral abdominal aortography and selective celiacomesenteric arteriography are essential for the evaluation of the proximal and distal portions of the celiacomesenteric arteries.

In some situations of "classical" abdominal angina, however, angiography may show no abnormalities. We have seen three patients who experi-

cnced no abdominal symptoms despite total occlusion of the celiac, superior mesenteric and inferior mesenteric arteries. The decompensated occlusion of vessels supplying the bowel is probably the cause of symptoms. Mucosal changes may be observed on barium studies, including luminal narrowing, "thumb printing" defects, and ulcerations. These changes may be followed by return to the normal appearance of the bowel or may be complicated by ulcerations, stricture and, rarely, gangrene of the gut.

Gastrointestinal Bleeding

It has been postulated that massive gastrointestinal bleeding in excess of 0.3 ml per minute must exist before contrast media is seen in the lumen of the bowel. The site and possible cause of the bleeding may be determined by celiac and/or mesenteric arteriography. However, we have failed to demonstrate the site and source of bleeding in several patients with massive, active gastrointestinal bleeding. Bleeding lesions such as gastroesophageal varices, gastric, duodenal and jejunal ulceration, aneurysms, angiomas, arteriovenous fistulas, and some tumors may be detected by celiac and/or mesenteric arteriography.

Recurrent, insidious gastrointestinal bleeding may be caused by angiodysplasias, as seen in the syndrome of Rendu-Weber-Osler, and by conditions which may cause hematobilia, such as following liver biopsies with complicating false aneurysms or arteriovenous fistula of the hepatic arteries. Angiodysplasias of the bowel and bowel tumors may be undetected by barium studies but discovered by celiacomesenteric angiographic examination. We have shown positive findings as frequently with recurrent chronic bleeding as with acute, massive, gastrointestinal hemorrhage.

Diverticulosis

Mesenteric arteriography is of particular value in bleeding diverticulosis. Barium enema will show diverticula but cannot establish the site of bleeding. When multiple colonic diverticula are present, inferior mesenteric arteriography can be of assistance in establishing which diverticulum (or diverticula) is the site of bleeding. Hence, unnecessary extensive surgery is avoided.

Gastrointestinal Tumors

It may not be possible to differentiate a benign from a malignant gastrointestinal tumor by arteriography. Deceptive findings may result from pancreatic carcinoma. Superselective arteriography and magnification technique enhance the angiographic demonstration of the abnormal neo-vascularity of gastrointestinal tumors. When celiac or mesenteric angiography reveals abnormal vascularity extending beyond the wall of the organ (except in cases of leiomyomas or abscesses), and when tumor vessels are observed in other abdominal organs such as the liver, in the bone, or in surrounding soft tissue, the diagnosis of a gastrointestinal malignancy may be suggested. We use routinely hepatic arteriography when a known malignant neoplasm is under evaluation to establish if liver metastases have occurred.

Pseudoneoplastic Changes

Pseudoneoplastic changes of the bowel may be observed on barium studies as a result of ischemic lesions. They are caused by edema and/or submucosal hemorrhage. Arterial or arteriolar occlusion and venous thrombosis may be the cause of these bowel abnormalities. Arteriography may reveal any of the following: *Normal arterial phase, occlusion of arterioles, prolonged arteriovenous circulation time, stasis in the arteries, delayed or absent venous phase, and complete avascular areas.* Whenever mucosal changes suggesting a carcinoma are observed in patients who have inflammatory disease of the large bowel, and when by arteriography we observe areas of ischemia, these patients should be treated conservatively, and a repeat barium study performed in a week or 10 days to establish the persistence of the process or possibly the regression of the changes. Surprisingly, rapid return to normality within one or two days may be observed in patients with suspected carcinoma of the bowel.

Granulomatous Disease

The differentiation between diffuse ulcerative colitis and granulomatous colitis is possible if one sees angiographic signs of arteriolar occlusion. This, however, is observed infrequently and only in the chronic stages of granulomatous colitis or in ischemic colitis. In the early stages of granulomatous enteritis either no angiographic abnormality will be seen, or increased, uniform vascularity similar to diffuse ulcerative colitis may be observed. When the large and small bowel appear involved angiographically, this finding would favor the diagnosis of granulomatous disease.

Pitfalls

Pitfalls in gastrointestinal arteriography may be seen in certain neoplasms such as pancreatic car-

cinoma. Some may be unrecognized because of minimal or absent neo-vascularity. Contrariwise, benign tumors, such as cystadenomas and some angiodysplasias, such as cavernous hemangiomas, may appear with increased, irregular neo-vascularity simulating a malignant neoplasm.

The most vascularized tumors of the gastrointestinal tract that we have observed are the endocrine tumors, such as insulinomas, Zollinger-Ellison syndrome, carcinoids, certain metastatic tumors (melanoma, renal cell carcinoma, angiosarcoma) and hepatomas. Certain inflammatory processes involving the bowel have neo-vascularity which may simulate that of a malignant neoplasia.

Conclusions

Thorough evaluation of diseases of solid organs, such as the liver, spleen, pancreas, kidneys, adrenals, and gonads, is made possible by the examination of their vasculature. Arteriography and venography are often combined and may reveal unsuspected processes affecting these viscera. When lymph-node involvement of the periaortic chain is suspected, retroperitoneal lymphography is the examination of choice and may be complemented by angiography. Advances in technology, such as the use of vasoactive compounds, new developments in catheterization instrumentation, magnification arteriography, and correlation with scanning, have expanded the possibilities and contribution of gastrointestinal angiography.

Tapeworms: or, What Have You?

If you have ever had the good fortune to meet a man carrying a pickled tapeworm, you should know that you have had an encounter with a descendant of an ancient line of specialists who work in the outlying faubourgs of medicine.

Originality often consists of inspired borrowing. The tapeworm trick went back for its inspiration to the surgical operation to remove calculi from the bladder, performed in the sixteenth century by wandering specialists called "stone cutters." They also operated for "stone in the brain." This procedure involved making an incision in the scalp and palming a "stone," as proof of results.

In the medical world of the patents the customer was always sure of a good show. Enormous tapeworms for exhibition purposes could be obtained for a modest consideration at any stockyard. Or an artifical worm, guaranteed to give satisfaction, could be purchased from a firm in Kansas City. If the worm turned out to be a "no show" it was explained that the medicine was so efficacious that it had dissolved the parasite.

The ready-made preparations offered to grow bushy hair on bald heads, make men more manly and women more womanly, quell the symptoms or "get at the cause," fix up that asthma, dyspepsia, or bronchitis—what a spectrum! There was once even a Commanding Oil. It made the meek strong and—well, commanding.*

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*Gerald Carson: One for a Man, Two for a Horse: A Pictorial History, Grave and Comic, of Patent Medicines.

Determinism

Naturally it is difficult to say precisely what role there is for determinism and precisely what role for free will. . . . Not long ago I heard a good definition of the relationship between free will and determinism. Someone compared it to a game of bridge. When the cards are dealt and you pick up your hand, that is determinism; there's nothing you can do except to play it out for whatever it may be worth. And the way you play your hand is free will.*

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*Jawaharlal Nehru, in Norman Cousins, Who Speaks for Man?

Legg-Calvé-Perthes Disease

FRANK S. BABB, M.D.* AND A. BRUCE SUNDBERG, M.D.*

Since "Perthes' disease" involves the epiphysis for the femoral head, a brief look at the femoral head would seem indicated. At birth the femoral head is entirely cartilaginous. The process of ossification begins during the second half of the first year of life. At puberty it is complete, and fusion to the metaphysis begins—a process usually not finished until the 17th or 18th year.

Anatomically, the femoral head forms two thirds of a sphere, but not a perfect sphere. It is normally somewhat flattened on top, where the acetabulum rests most heavily upon it. It is directed medially, upwards and forwards, in such a manner that the anterior part is *not* engaged in the socket when we are in the standing position. (This may have real significance in the "saddle deformity" so frequently seen in Perthes' disease.)

From the end of the first year of life until puberty, when ossification of the femoral head is complete, the blood supply to this organ varies in a most interesting manner. It is, in fact, precarious. Little or no blood supply has as yet developed in the ligamentum teres. The nutrient vessels have not crossed the epiphyseal plate. This leaves the retinacular vessels as the only dependable blood supply and, as Trueta points out, only the posterosuperior group may be functioning effectively at this age.

Up to three years of age, fortunately, this epiphysis is small, the demands made upon it are slight, and its vascular requirements are meager. Beginning at four years of age, however, the proximal femoral epiphysis is being subjected to more and more activity (particularly in boys). These ever-increasing demands, plus its increasing size, may now constitute a disproportion between the volume of the vascular tree and its contents—a state of relative avascularity.

By 10 years of age, the retinacular blood supply has improved, the foveolar vessels are by now anastomosing with them, and very shortly the nutrient vessels begin to cross the epiphyseal plate. The precarious period of vascular insufficiency is now over, provided these vascular channels are not subsequently disrupted.



Fig. 1—Femoral Head

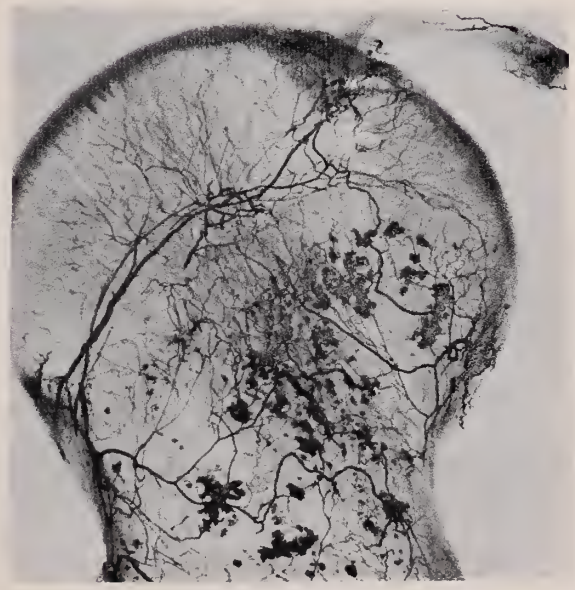


Fig. 2—Retinacular Epiphyseal Vessels.

*Gillette State Hospital, St. Paul, Minnesota.

Clinical Picture

It is not surprising then to read descriptive accounts of an intermittent limp occurring in children from four to eight years of age, with an insidious onset, minimal pain, occasionally referred to the knee, predominantly in males (five to one) and relieved by rest in recumbency. Physical examination early reveals a limitation of internal rotation in the hip, and possibly abduction. Pain is present in the extremes of motion and the hip becomes more and more limited if untreated. It also seems worthy of note that these children frequently exhibit a growth retardation.

This, then, was the condition described independently in 1910 by Arthur Legg in America, Jacque Calvé in France, and George Perthes in Germany. They separated it as an entity, differentiated it from tuberculosis, and inadvertently gave it the name Legg-Calvé-Perthes disease—or as Dr. Goff suggests, Legg-Calvé-Perthes syndrome.

Etiology

Many various etiological causes for this condition may have been proposed, and not without good reason. Goff suggests it is a multi-system syndrome. At times, the condition even appears to occur in epidemic form, and it seems reasonable to believe that many external influences may effect the blood supply to the proximal femoral epiphysis. Of these, however, the easiest to accept would have to be trauma. In any event, there is almost uniform agreement that the condition represents an avascular necrosis of the proximal femoral epiphysis and its metaphysis. It is interesting to note that many authors have observed the low incidence of this condition in Negroes. Trueta was able to demonstrate that in the negro race a significant anastomosis between the foveolar and the retinacular vessels existed throughout childhood, which might well explain this observation.

Recent experimental studies on the influence of intra-articular pressure reveal that the maintenance of such pressures above 70mm. of mercury will produce avascular necrosis of the femoral head in experimental animals. This might seemingly explain the so-called "non-specific synovitis of the hip," which sometimes completely resolves with temporary bedrest and traction, and yet other times recurs, only to go on to a full-blown avascular necrosis of the proximal femoral epiphysis. It is tempting to postulate a relatively minor trauma resulting in synovial effusion of the hip and pressure occlusion of the retinacular vessels. Subsequent developments would then vary with the degree and the duration of the abnormal intra-articular pressure.

Pathology

It was formerly taught that the dense white "wafer" atop the femur was a soft necrotic head which became gradually deformed with or without weight bearing. It is now apparent, however, that death of the head occurred long before the dense white epiphysis made its appearance and, although the ossific nucleus dies, the cartilaginous model for the femoral head survives. During revascularization of the cartilage model, the latter is described as "biologically plastic" and, provided the model can be prevented from deforming, a new spherical femoral head can hopefully reossify.



Fig. 3—"Dense White Wafer."



Fig. 4—Early Necrosis

Radiological Features

The earliest radiological indication of avascular necrosis is cessation of growth in the ossified part of the femoral head. This obviously will be a very subtle change at first and must be looked for carefully. When present, this means that the head has been avascular for quite some time, and

what we see from then on is the revascularization of the dead head, and the biologically plastic cartilage model. The appearance previously described as "fragmentation" is in reality reossification of the cartilage model, and fragmentation is *not* a good term. As reossification occurs, the previously unossified parts of the cartilage model begin to appear on the x-ray, and if portions of this model head are outside the limits of the acetabulum, then a "bump" develops and a typical saddle-shaped deformity eventually appears on the x-ray. What we are actually looking at is the reossification of two femoral heads, one within the acetabulum, and one outside the acetabulum. Another interesting phenomenon is the so-called "head within a head," which occurs when previously unossified cartilage surrounding the original ossific nucleus becomes ossified.



Fig. 5—"Fragmentation"—Poor Term.

Prognosis

There appear to be three factors that influence the prognosis. First, the younger the child, or the closer to five years of age the child is when the disease develops, then the better the prognosis. It has been suggested that in the younger child the femoral head is smaller, and therefore there is less volume to reossify. In any event, children who develop Legg-Perthes disease prior to five years of age heal faster and with less deformity



Fig. 7—"A Head Within a Head."

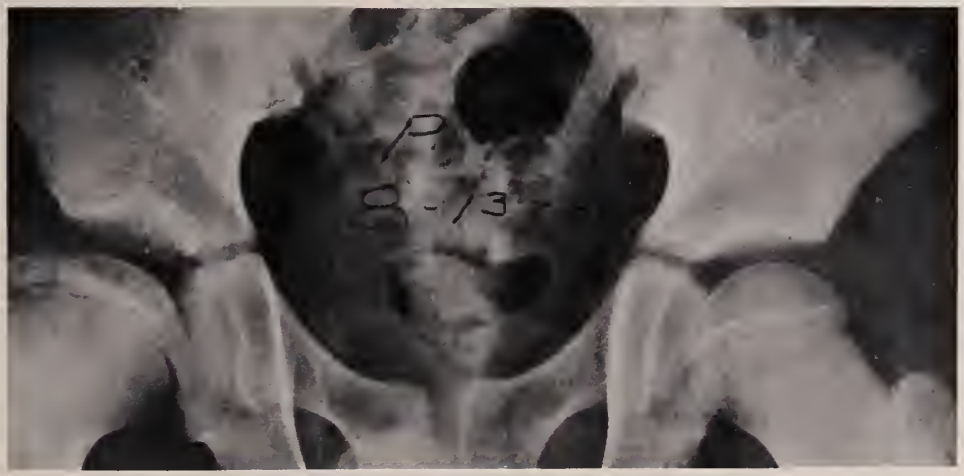


Fig. 6—Two Femoral Heads.

than children beyond six years of age.

Secondly, the degree of involvement of the femoral head also seems to influence the prognosis. If only part of the femoral head undergoes avascular necrosis, there is much less resulting deformity. Conversely, if there is total involvement of the femoral head, and particularly if cystic changes are present in the metaphysis, then the prognosis is much worse, and the tendency is towards a poor long-term result.

Finally, the earlier the child is seen in the course of the disease is important. If joint deformity has already occurred, the opportunity to obtain a good result has passed.

Treatment

If one subscribes, therefore, to the theory of biological plasticity in a slowly reossifying cartilage model, then the management of this self-limited disease becomes obvious.

The plastic femoral head must be retained within the mold of the acetabulum, and it will reossify in a spherical manner. Conversely, if part of the plastic head is constantly allowed to remain outside the limits of the acetabulum, then a saddle, a mushroom or a double femoral head is almost bound to develop. The only position in which the spherical head of the femur is completely within the mold of the acetabulum is in



Fig. 8—Total Involvement.



Fig. 9—Traction, Abduction, and Internal Rotation.

moderate abduction, internal rotation and slight flexion. The benefits of bedrest with *traction* during the initial phases of the disease, we all accept. Preferably, this is carried out with the hips abducted, slightly flexed, and when possible, internally rotated. It seems no longer necessary, however, to confine these children to many months, and sometimes years, of bedridden invalidism, once the synovial reaction has subsided. This may require several days or several weeks; but once a full range of motion has returned, various means are available for maintaining abduction and flexion of the hip joints, as suggested.

can only be determined by an arthrogram.

Dr. Axer in Tel Aviv, and Dr. Abrams of Baltimore, have attacked the problem from the opposite side of the joint and carried out a subtrochanteric osteotomy, in order to better center the head within the depths of the acetabulum and insure complete and constant coverage of the biologically plastic epiphysis. Finally, in older children with deformed femoral heads, resulting from Legg-Perthes disease, arthroplasty may eventually be necessary to relieve pain and improve range of motion.

One would hope, however, that with early



Fig. 10—Craig Bar.

Based on the broomstick cast principle, the use of an abduction bar, such as devised by Dr. Craig, or the Toronto Legg-Perthes brace, permits early ambulation with crutches. In addition, the brace must be worn at night, as well as the daytime, until reossification is complete. More recently, a trilateral socket brace has been advocated and is being investigated by Dr. Tahchdjian.

Later in the disease, when subluxation of the hip has existed for some time, more extensive measures may be necessary. If bedrest and traction fail to restore a normal range of motion, then surgical release of the soft tissue must be carried out. This may include a psoas tenotomy. The extra-articular portion of the femoral head must be covered by the acetabulum. When adequate coverage cannot be accomplished otherwise, an innominate osteotomy, according to the method of Salter, should be considered. In Dr. Salter's hands this has proven an effective measure, with encouraging results, provided the deformity of the femoral head has not already occurred. This



Fig. 11—Complete Coverage.

diagnosis and proper positioning of the hip joint in the early stages, such surgical measures would prove unnecessary. Meanwhile, the notoriously poor results of no treatment, Sam Brown belts, ischial weight-bearing braces with Patten extension, and bone drilling operations, lead us to believe that "there must be a better way." We presently subscribe therefore to the theory of complete, uninterrupted acetabular coverage of the femoral head by whatever means proves necessary. Preliminary traction followed by an abduction bar is presently our treatment of choice.

Pathological Fallout

How knowledgeable and insightful will the future medical historian have to be to assess in retrospect the complexly reciprocal interaction between a statesman's pathologies and his political policies whereby the course of history is determined! This compelling challenge is presented by Hugh L'Etang in his *The Pathology of Leadership.*

"The historians of the first half of the twentieth century plotted new territory as they put Churchill under the microscope. The historians of the second half of the century can explore a new dimension if they use a high power lens and simultaneously chart Churchill's decisions and actions with his mental and physical state. Could it be that the magnificent failure at the Dardanelles in 1915 was conceived in elation and executed in depression or conceived in depression and executed in elation? Was the tempo of Government slowed or altered when he was afflicted by Black Dog? Can changes of mood explain the enthusiastic appointment of Auchinleck in 1941 and the ungenerous dismissal in 1942; or account for the optimism about the Anzio landing and the pessimism about the Normandy landing in 1944? Was the exuberance of elation cancelled out by the lethargy of depression or did neither of these extremes have any noticeable effect on those devoted servants who control the elaborate machinery of the ship of State? One day we may know how many vital decisions were taken by Churchill in an hour, in a day, in a week and in a month; and how these decisions were influenced by sickness and health, M and B and mepacrine, boredom and excitement, austerity or indulgence, frustration or fulfillment, and envy or contentment. The questions are not idle ones and the gaps in our knowledge call for serious study rather than academic speculation. Drugs are now available that can stimulate those who are depressed and quieten those who are elated. Drugs are available that can alter perception and distort the patterns of thought and reason. Nor must one forget the everyday drugs that are used for trivial illness which can have unexpected and untoward effects on the mind. The task of a future Moran (Churchill's doctor) is a daunting one for he will need to know as much about the machinery of government and international relations as he knows about the machinery of mind and body if he is to discharge properly his crushing obligations."*

---

*Hugh L'Etang: The Pathology of Leadership, 1970.

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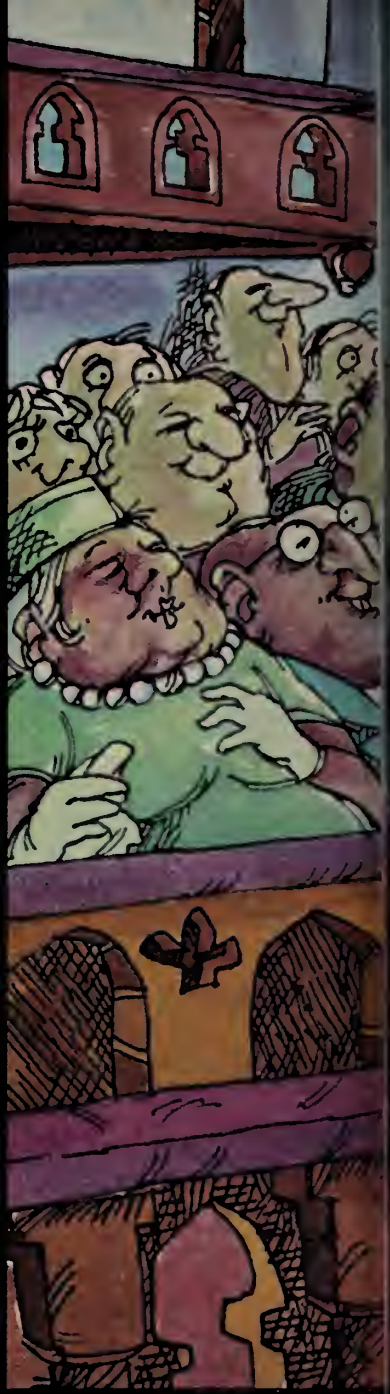
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1. Demeulenaere, L.: Action du R 1132 sur le transit gastro-intestinal, Acta gastroent. Belg. 21:674-680 (Sept.-Oct.) 1958.

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5-8 yr.....1 tsp. q.i.d. (8 mg.)
8-12 yr....1 tsp. 5 times daily (10 mg.)
Adults:....2 tsp. 5 times daily (20 mg.)
or 2 tablets q.i.d.

*Based on 4 cc. per teaspoonful.

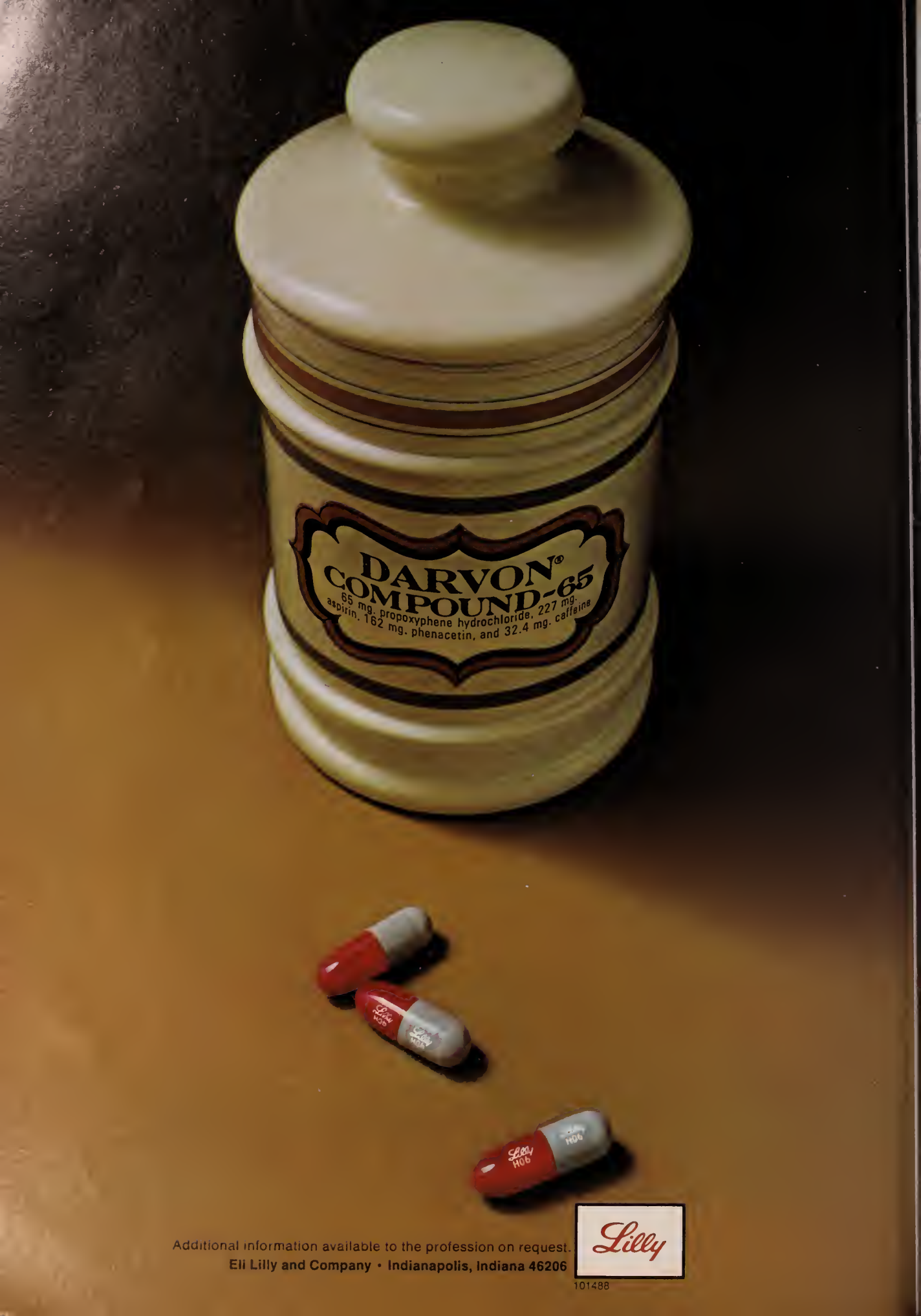
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Editorials

Elective Sterilization

THE ACCEPTANCE OF surgical sterilization by both the medical profession and the patient community in the last two years has been encouraging. Most hospitals in Minneapolis in the last year have deleted the necessity of committee review for approval of sterilization procedures, leaving the choice quite properly with the patient and her doctor. The response has been nothing short of overwhelming.

It would be safe to say that the average female has at least 15 years of fertility remaining when she has the size family that she and her husband desire. There is no reason for her at this time to accept the risks of failure or the medical risks of the reversible methods of birth control. The choice at this point is which surgical method is preferable.

If the patient and her husband have made the decision for surgical sterilization at the time of delivery of their last child, an extremely simple procedure is possible that adds essentially no morbidity to the normal post-partum convalescent period.[1] Having missed this opportunity, the obvious procedure of choice had been vasectomy.

With the recent addition of laparoscopic tubal ligation,[2] the female now has the choice of a procedure of equally low morbidity. When vasectomy and laparoscopic tubal ligation are compared, the only real difference is that laparoscopy requires general anesthesia and its inherent risks, as compared to local anesthesia. This seemingly would be enough to sway the balance toward vasectomy, which is certainly the case in many situations. However, every patient has her own individual needs to consider.

Not every male is able to accept vasectomy. A woman with a specific medical indication should be the one who has reproductive capacity terminated. Also, one should not forget the age we live in, and realize that many women in their reproductive years are going to have more than one partner. Pregnancy still remains the burden and responsibility of the female regardless of circumstances of conception.

Problems arise, however, in imp'ementation of this procedure. Because this is an unfamiliar technique to most practicing gynecologists today, there is a need for basic courses in laparoscopy in local teaching institutions. Pressures, also, need to be placed on insurance companies to recognize the need for elective sterilization procedures to constitute an accepted area of coverage.

David L. Hill, M.D.
Minneapolis, Minnesota

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SCH-2654

Recognition and Management of Tricuspid Valve Disease in the Presence of Mitral Valve Disease*

The clinical recognition of tricuspid incompetence ordinarily is accomplished at the bedside without difficulty and can be verified by cardiac catheterization. The diagnosis, on the other hand, of tricuspid stenosis is difficult both at the time of clinical examination and at the time of hemodynamic studies.

When the findings are those primarily of tricuspid stenosis with or without incompetence, the diagnosis is organic tricuspid disease, and management is total valve replacement. On the other hand, in the patient with mitral valve disease who presents with significant and predominant tricuspid incompetence, the problem of differentiating functional tricuspid regurgitation from organic tricuspid involvement becomes most difficult.

Several clinical observations suggest functional tricuspid incompetence. Relative or functional tricuspid incompetence is due to a dilated tricuspid ring in the presence of normal tricuspid leaflets and supporting structures. This form of tricuspid regurgitation is of a dynamic nature and will improve with aggressive treatment of congestive heart failure, which often requires hospitalization and observation. Functional tricuspid incompetence is a result of long-standing pulmonary hypertension complicating mitral valve disease, which results in right ventricular hypertrophy and, ultimately, right ventricular dilatation and right heart failure. The presence, then, of pulmonary hypertension on clinical examination favors a diagnosis of relative tricuspid incompetence.

The patient with long-standing mitral valve disease who has significant tricuspid incompetence in the face of pulmonary hypertension, who has no evidence of tricuspid stenosis on physical examination or at the time of hemodynamic studies, if these are done, or who improved with treatment after hospitalization most likely has tricuspid incompetence of a dynamic or functional nature.

Because of the difficulty of assessing the tricuspid valve before operation, it has been our practice at the Mayo Clinic to palpate the tricuspid valve in every patient undergoing open mitral valve surgery. Routine hemodynamic evaluation of the tricuspid valve is therefore not necessary during the preoperative evaluation of the patient.

The various surgical techniques used for the correction of functional tricuspid incompetence have met with varying success. At the time of this writing we have had the greatest success with a type of annuloplasty that obliterates the posterior cusp and converts the valve into a biscuspid valve. The heart is allowed to beat; the right ventricle is then filled with blood, and competency of the valve can be inspected under direct vision. This adds relatively little time to the operation and long-term results have proved this method satisfactory.

The authors consider it important to perform some type of annuloplasty in all cases in which the functional tricuspid insufficiency is of moderate to severe degree. The postoperative cardiac output is improved, and the convalescent period is thus shortened. It is possible that this procedure has led to survival of a few more patients who would otherwise have died of low cardiac output. Also one avoids the situation of the occasional patient who has disappointingly poor results from mitral valve surgery because the tricuspid insufficiency fails to regress spontaneously or, in some instances, even progresses over a period of observation.

Although there is no unanimity of opinion regarding the proper management of functional tricuspid incompetence in the face of long-standing mitral valve disease, in our opinion a middle-of-the-road approach offers many advantages over the "do nothing" approach on the one hand or total valve replacement on the other.

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Gordon K. Danielson, M.D.†
Rochester, Minnesota

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†Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

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Neutral Gastric Antacids

The papers by Dr. Ansari[1] and by Dr. Piper[2] and the comments thereon by Dr. Hoffman[3] and by Dr. Gambill[4] prompt me to attempt to bring to the attention of your readers the fact that neutral gastric antacids that cannot produce systemic alkalosis or even a neutral or alkaline stomach, nor lead to phosphate depletion, were reported by me in 1923[5]. They are $Ca_3(PO_4)_2$ and $Mg_3(PO_4)_2$ in such proportions as will, in the particular patient, be neither constipating nor laxative. A clinical report on their use by the late John L. Kantor[6] appeared in the same year. These substances, and $Ca^{++}PO_4$ and $MgHPO_4$, which are also effective, failed of adoption because they could not be advertised under a proprietary name in the standard medical journals. However, their efficacy led to the appearance of a host of neutral gastric antacids. In my opinion, none of these are any better and some are dangerous.

Isidor Greenwald*
New York, New York

*New York University Medical Center, School of Medicine, Department of Biochemistry.

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Australia Antigen

It is unfortunate that prior to publication of the editorial by Dr. J. N. Mork* apparently no effort was made to contact those individuals in the state who are in fact most concerned with blood banking. In May of 1970, the Minnesota Association of Blood Banks presented a symposium at the Mayo Clinic on hepatitis in which Dr. Prince and Dr. Grady presented papers. The Mayo Clinic Blood Bank, University of Minnesota Hospital Blood Bank and the Minneapolis War Memorial Blood Bank have been routinely screening donors for Au antigen since early in 1970 and some of these banks have been doing testing for an even longer period than that. Dr. Howard Taswell of the Mayo Clinic Blood Bank has published several articles on the use of Australia antigen in detecting hepatitis carriers among blood donors.† I would also like to inform you that the availability of adequate reagents, the Minnesota Association of Blood Banks in cooperation with the Minnesota State Medical Association Committee on Blood Banks is setting up training programs, proficiency testing, and a statewide registry of Au antigen positive donors.

I only hope that next time a question concerning what the blood banks in Minnesota are doing someone would contact us.

Herbert F. Polesky, M.D.‡
Minneapolis, Minnesota

*Minnesota Med 54.43, 1971.
†JAMA 214:142, 1970.
‡Director, War Memorial Blood Bank, Minneapolis.

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Counterfeit Physicians?

Collectivist demagogic tyrants and politicians down through recorded history have made expansive gilded promises of "something for nothing" appealing to those in their population who thought they would "come out ahead" at the expense of the next guy.

History also records that when it came time for these ancient rulers to redeem their glowing promises they attempted to do so by debasing the coin of the realm and imposing strict controls to force acceptance of the new counterfeit coin. They failed. There were no Utopias.

Currently, we see our collectivist, demagogic, tyrannical rulers promising as an inalienable right free comprehensive cradle-to-grave medical care in addition to promising ....., ..., ..., etc. (You fill in blanks to suit.)

Free at whose expense? But I mustn't get too involved. The rulers found that it was impossible to redeem their promises even with confiscatory taxation, so now we see modern versions of age-old techniques, that is, controls and counterfeit coin in the form of inflation (increasing paper and token money supply which the rulers will not redeem nationally or internationally in gold; gold being such a "BARBAROUS RELIC" the rulers greedily control it all "for our protection").

It appears, however, that in attempting to redeem their promises regarding medical care, the rulers have discovered that counterfeiting coin alone was inadequate. Therefore, the rulers have sanctioned and embarked upon a "bold and imaginative" scheme—to counterfeit physicians: The assistant physician, the Medico, et al.

Caveat Emptor!

James J. Diehl, D.D.S., M.D.
Minneapolis, Minnesota

Apostles' Creed

I agree with the Montreal physician who considered Dr. Bethune's parody on *The Apostle's Creed was "sacrilegious." It does not seem fair to me that an organization to which I have faithfully paid dues for 23 years and supported, should redicule the faith of us Christian members—not even if Dr. Bethune is the same who passed me in my oral exams for the AMCP.**

Lillian A. Olson, M.D.
Ah-Gwah-Ching, Minnesota

*Minnesota Med, 10:819, 1971.

Editor's Note: The oversight was my error, and I apologize most humbly. I would not want to injure the image of MINNESOTA MEDICINE. *I beg to be forgiven.*



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Editor's Soliloquy

It's Been An Education

SINCE MY MANDATORY RETIREMENT as Editor, and my conviction without trial, I have been having some difficulty in formulating my last official Editor's Soliloquy. I am tempted to vent my spleen, garnish it generously with bile, and then ignite it with flaming invectives, but I guess I'll just come out of my corner looking, if not feeling, like a lamb and try to smell like a rose.

For eleven years I have had a great time and you have been a wonderfully receptive audience. I have learned to know that medical men are, on the whole, the greatest on earth; they are true humanitarians; they love people and are sincerely dedicated to the welfare of mankind, rich and poor, black and white, Christian, Jew and heathen.

I have never known one of you who would not—and most of you have—risk your life for the life and health of your patient. You are, indeed, individualistic with many differences of opinion, but in a pinch you invariably yield if the welfare of those whom you serve is at stake.

You have the same physical weaknesses as other people, but you never complain of your own misfortunes.

You are occasionally misunderstood or misrepresented, but I feel assured that your interest in your individual patient is always genuine, sincerely scientific, and within the framework of your knowledgeable ability. It would be extremely rare to encounter a physician who was carrying out any operation or procedure without confidence that he is capable of doing it.

The gamut of emotions of others has been showered upon you from time to time, but your persistence in doing what is right has never diminished or appreciably deviated from your original goal of serving.

Without these virtues medicine could not have prospered or advanced to the heights that it has reached.

Currently popular innovations for the medical men are being toyed with. Guard the lofty, scientific and intellectual profession that you represent. Let it not falter. Do not allow its noble character to decline, for you cannot afford to fail society by dispensing service less qualified than that which your and preceding generations have developed.

Be intellectuals; be proud of your heritage in being in the medical center of international recognition; expend your efforts and your dues for educational advancement; be in all things fair in your dealings and be above the petty jockeyings that infiltrate our society; practice the virtues; be noble, honorable men and women.

L'Envoi!

Carl O. Rice, M.D.
Editor-in-Chief

OLD DOC HESS SAYS: If you are looking for a fault in a man, it is not hard to find; everything he does is wrong.

The man who questions opinions is wise; the man who quarrels with facts is a fool. —Frank Garbutt

---

There are very few things in the world which it is worthwhile to get angry about, and they are just the things that anger will not improve. —Henry Jarvis Raymond

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Case Report

Gastrocolic Fistula Due to Benign Gastric Ulcer

COUNCIL MILLER, M.D.* AND JOHN P. DELANEY, M.D., Ph.D.*

SPONTANEOUS COMMUNICATIONS between the stomach and colon have varied origins. The commonest type of fistula is gastro-jejuno-colic secondary to stomal ulcer following a gastro-jejunal anastomosis. Direct gastrocolic fistulas most often develop through malignant lesions of the colon or stomach. Less frequently, they occur in association with operation, regional enteritis, intestinal tuberculosis, intraperitoneal abscess, trauma, perforated colonic diverticulum, chronic ulcerative colitis, and benign gastric ulcer. We recently dealt with a case of a gastrocolic fistula secondary to benign gastric ulcer and were prompted to review the experience at the University of Minnesota Hospitals. Our records failed to uncover another instance of gastrocolic fistula due to benign gastric ulcer. Forty such cases were found in a literature search. Twenty-four of the 40 were reported prior to 1903 in a review by Verbrugge.[15] The purpose of this communication is to detail another case report and to review the more recent literature on this topic.

Case Report

A 57-year-old Caucasian woman with Felty's syndrome (rheumatoid arthritis with splenomegaly and leukopenia) complained of a chronic knee ulcer and arthritis. She had been treated for rheumatoid arthritis with aspirin and gold injections for many years. Approximately a year prior to this admission she had developed nausea, vomiting, hematemesis and loose, tarry stools.

Previous Surgery

After repeated bouts of gastrointestinal hemorrhage, an exploratory laparotomy was performed at another hospital, where a mass was found associated with the midbody of the stomach, fixed posteriorly to the pancreas and inferiorly to the colon. The surgeon considered the lesion to be an unresectable carcinoma of the stomach. No tissue verification was obtained and no further procedures were carried out. After surgery the patient was treated with a course of 5-Fluorouracil. On conservative ulcer management she remained asymptomatic with regard to the gastrointestinal tract for the next year. Her private physician treated her for arthritis with monthly 20 mgm. injections of depot methylprednisolone acetate over the preceding eight-month period.

Initial Findings

Admission diagnoses included Felty's syndrome, hypothyroidism, peripheral vascular disease with a left iliac block, and a chronic ulcer overlying the left patella. Upper gastrointestinal x-rays showed some narrowing at the mid-body of the stomach which was thought to be secondary to old ulcer disease or surgical deformity. Neither an ulcer crater nor a malignancy was identified. After two weeks of in-hospital therapy with buffered aspirin, 1.2 grams every four hours, for rheumatoid arthritis, the patient complained of diffuse abdominal pain and developed intractable diarrhea which lasted for four weeks. The stools were liquid yellow, numbering six to 12 per day, and frequently contained undissolved capsules of medication taken in the previous hour. Barium enema examination three weeks later demonstrated contrast medium entering the stomach from the left transverse colon. No tumor could be identified in the colon. Gastroscopy at this time showed a greater curvature ulcer with stool and barium emanating from the base but no evidence of tumor in the stomach. Gastric secretory studies yielded no base-line free acid and a peak of 3.7 mEq. of acid per 30 minutes following histolog administration.

Preoperative Management

At the time of transfer to the Surgical Service, the patient had lost 13 pounds during five weeks of hospitalization. Total serum proteins were 5.6 gm.% with an albumin of 2.4 gm.%. The hemoglobin was 10.4 gm.%. She was prepared for surgery with a one-week course of parenteral hyperalimentation. Antibiotic and mechanical bowel preparation was also carried out.

Surgical Repair

A limited laparatomy was done under local anesthesia to construct a transverse colostomy. Some induration could be felt in the area of the gastrocolic fistula, but no evidence of tumor was found. Colostomy as the first of a two-stage procedure was chosen because of the patient's extreme debility and multi-system diseases.

Almost as soon as the patient resumed oral alimentation, she began to gain weight. The ulcer on the knee, which had been present for over two years, completely epithelialized. Four months later, following a marked improvement in general condition, a two-thirds distal gastrectomy was done with a segmental transverse colectomy, to include the area of the fistula. The transverse

*Department of Surgery, University of Minnesota Hospitals, Health Sciences Center, Minneapolis, Minnesota.

TABLE

Author	Age/Sex	Predisposing Factor for Gastrocolic Fistula	Site of Gastric Ulcer	Treatment of Fistula	Postop Progress
Firth 1920 (6)	51 M	None	LC	Discovered at Autopsy	No Operation
Wilkie 1934 (16)	32 M	None	LC	2-Stage Resection	Recovered
Pein 1948 (13)	5 wk M	?	GC	Suture Closure	Died
Briggs 1952 (3)	58 M	None	LC	1-Stage Resection	Recovered
Bosien 1952 (2)	45 M	Chronic Steroid Therapy	GC	1-Stage Resection	Recovered
Gray 1955 (10)	35 F	None	GC	2-Stage Resection	?
Bachman 1955 (1)	33 F	Chronic Steroid Therapy	LC	Suture Closure	Died
Deshpande 1964 (4)	56 F	Suture Closure of Perforated Gastric Ulcer	LC	1-Stage Resection	Recovered
Smith 1965 (14)	54 M	None	GC	1-Stage Resection	Recovered
Lang 1965 (10)	52 F	None	?	Suture Closure	Died
Lazar 1966 (11)	54 F	None	GC	1-Stage Resection	Recovered
Lewis 1966 (12)	47 F	None	?	1-Stage Resection	Recovered
	45 M	Chronic Steroid Therapy	GC	1-Stage Resection	Recovered
Hoffman 1966 (9)	49 F	Chronic Steroid Therapy	GC	1-Stage Resection	Recovered
Ganji 1967 (7)	65 M	None	GC	2-Stage Resection	Died
Dotson 1968 (5)	52 F	None	GC	1-Stage Resection	Recovered

colon and greater curvature of the stomach were densely adherent. The site of the previous fistula tract was readily apparent. Pathologic examination of the specimen showed that the gastrocolic fistula had completely healed. The colon was reanastomosed end-to-end and a Polya-type anastomosis was made between the stomach and jejunum. The postoperative course was uneventful. The patient has continued to gain weight and has had no gastrointestinal symptoms since that time.

Discussion

The Table lists the individual cases of gastrocolic fistula due to benign gastric ulcer reported in the English literature from 1920 to the present. Pertinent to the present case report, Bosien and Tyson[2] reported spontaneous perforation of a benign gastric ulcer into the transverse colon of a patient who had been taking cortisone acetate and ACTH for rheumatoid arthritis. Bachman and Rogers[1] in 1955 reported a similar case: a 33-year-old woman who had been on chronic corticosteroid therapy for psoriasis and psoriatic arthritis. Lewis[12] and Hoffman[9] both described patients on prolonged steroid therapy who developed spontaneous gastrocolic fistulas.

Gastrocolic fistula secondary to benign gastric ulcer is an unusual condition. Of 16 cases reported this century, five, including the present, have been associated with prolonged adrenal corticosteroid therapy. Because of the complicating medical problems and cachexia in this particular patient, we chose a two-stage approach beginning with a transverse colostomy. The response to diversion of stool away from the upper gastrointestinal tract was striking. The patient regained appetite, rapidly gained weight, and was able to ambulate for the first time in months. The biologic importance of improved nutrition was demonstrated by the rapid healing of a chronic leg ulcer. We were surprised to note the complete healing of the gastrocolic fistula and are unaware of this having been reported before. A history of recurrent gastric ulcers and the necessity for continued arthritis medications obviated any thoughts of non-resectional therapy in dealing with this problem, even with the fistula healed.

Summary

A case is reported of a gastrocolic fistula due to benign gastric ulcer associated with prolonged steroid therapy. This is the only recorded case in which the fistula healed following a diverting colostomy.

References may be secured from the author or the reprints.

People who can't keep from criticizing the younger generation usually can't remember who raised it.





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Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely necrotizing vasculitis, paresthesias, icterus, pancreatitis and xanthopsia have occurred with thiazides alone.

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Fracture Conference

Early Mobilization after Spinal Cord Injuries*

FOR THIS FRACTURE conference we wish to discuss a method of treating spinal fractures with emphasis on early mobilization. Some of the physiologic effects of immobilization in the paralyzed patient will be mentioned.

Presentation of Cases

The first patient is a 16-year-old boy who, on July 19, 1968, dove into shallow water and immediately experienced paralysis and loss of sensation below the shoulders. He was retrieved from the water by his siblings and was taken to a local hospital, where he underwent emergency x-ray examination and was placed in head-halter traction. Soon after this evaluation, he was transferred to a Rochester hospital by ambulance. On admission he was recovering some feeling in his arms and he could tell when his legs were being moved. The first roentgenogram (Figure 1 *A*) in Rochester showed a fracture of C_{-4} and C_{-5} with anterior displacement of C_{-4}.

Emergency Treatment

In the emergency room the patient was placed in Crutchfield tong traction, a three-way catheter was placed in his bladder for irrigation, and a lumbar puncture was done which showed no block with jugular pressure. The case was discussed and the attending neurosurgeon felt that a laminectomy was not indicated at that time.

Progress

For two days the patient continued to improve and developed a sensation of touch to the level of T_{-4} and vibratory sensation in all extremities. Serial roentgenograms made while he was in traction showed good alignment of the fracture. Several days after injury a myelogram showed no block to the contrast medium at the level of C_{-4} and C_{-5}. Five days after injury his motor function was assessed as being at the level of C_{-5}. Three weeks after injury his neurologic status became stable, and a neck-stabilization procedure (fixation from C_{-3} to C_{-6}) was done using Williams plates.

Rehabilitation

The attending orthopedic surgeon felt that the stabilization procedure would be valuable in allowing early rehabilitation, which was started in the Department of Physical Medicine and Rehabilitation. The parents were told that the rehabilitation of a tetraplegic requires approximately one year of hospitalization. However, they felt that this was not necessary and the patient was taken home two and one-half months after injury, when his motor function level was at C_{-8}.

Reevaluation nine months after injury disclosed spotty return of motor function in his upper extremities. On the right the extensor digitorum longus, extensor carpi radialis longus and brevis, brachioradialis, flexor carpi ulnaris, adductor pollicis and pronator teres were weak. He had triceps function. Function on the left side was similar. Improvement was rapid enough so that reconstructive tendon transfers in his hands were not thought to be indicated at that time. Roentgenograms demonstrated that the patient was quite stable with the Williams plate in position (Figure 1 *B*).

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*Fracture Conference on June 9, 1969.

The second case is that of a 44-year-old man who, on December 29, 1965, was pulled into some gears at a grain elevator when his coat sleeve was caught in the machinery. He was drawn in up to his axilla, his neck was hyperextended and rotated, and he had third-degree burns of his left axilla. He was taken to a local hospital. On admission he could move both legs. He was kept overnight and the next morning he was quadriplegic. Skull traction with tongs was instituted, his condition was allowed to stabilize, and three weeks after injury he was transferred to Rochester. A roentgenogram (Figure 2 *A*) demonstrated a fracture of the posterior elements of C_{-6} with posterior dislocation of C_{-6} and C_{-7}. He had no motor function below the C_{-7} level. Five weeks after injury, on February 2, 1966, a myelogram indicated a complete block; therefore laminectomy and fixation with Williams plates were done. Five days after the stabilization procedure on the cervical spine he was transferred to the Department of Physical Medicine and Rehabilitation for treatment.

On January 30, 1967, he had the first stage of a Henderson-Lipscomb procedure for tendon transfers in the tetraplegic hand. In March 1967 he went home and has not returned as yet for surgery on the other hand.

The third patient is a 19-year-old nursing student who was in an automobile accident in November 1966. She was given emergency care locally and transferred to a Rochester hospital. When she arrived she had an indwelling catheter in place and no function in either leg. X-ray examination showed a fracture of the body and lamina of T-12 (Figure 3 *A*). She was taken to the operating room for a laminectomy and decompression, where it was found that the conus and the cauda equina were completely transected. At the time of decompression she underwent stabilization of the lumbodorsal spine with Williams plates (Figure 3 *B*). As is seen in Figure 3 *B*, because of the configuration of her spine and her slight build, the plates were fairly close to the skin. Two weeks later she was transferred to the Department of Physical Medicine and Rehabilitation for training. When dismissed she was able to walk with long leg braces and to take complete care of herself. On April 8, 1967, the Williams plates were removed because they were irritating the skin.

Discussion

Dr. Joachim Opitz:

The following comments on some of the effects of prolonged immobilization are based in part on well-controlled studies of immobilized healthy young men,[1,2] in part on studies done on patients with varying degrees of paralysis



Fig. 1—Cervical spine of a 16-year-old boy with tetraplegia. *(A)* Lateral view at admission. Picture was taken with patient in head-halter traction (10 lb.) and shows fracture of C-4 and C-5 with posterior displacement of C-4. *(B)* Lateral view approximately 10 months after stabilization with Williams plates from C-3 to C-6.

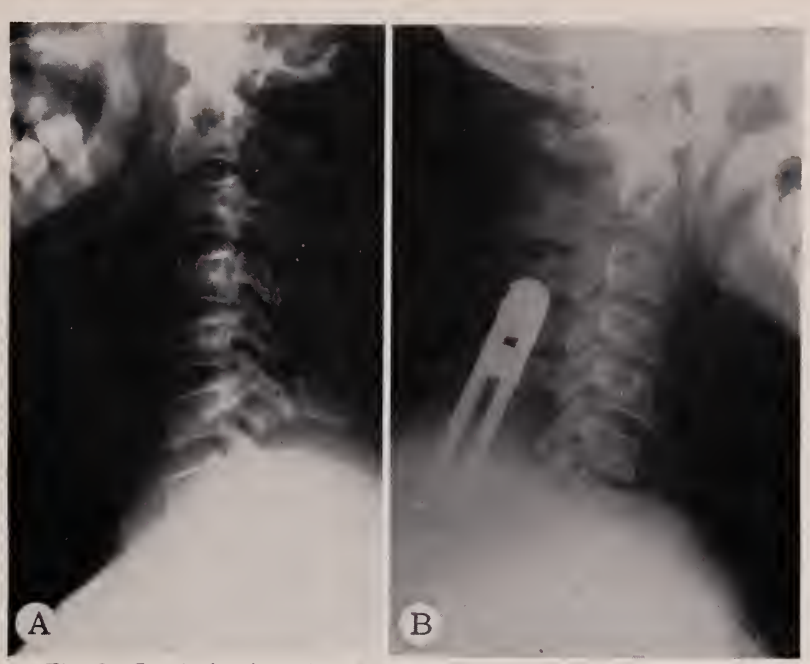


Fig. 2—Cervical spine of a 44-year-old man with fracture-dislocation of C-6 on C-7. *(A)* Lateral view approximately one month after injury and treatment elsewhere in tong traction and skeletal traction. *(B)* Lateral view two months after insertion of Williams plates to stabilize C-6 and C-7 fracture-dislocation.

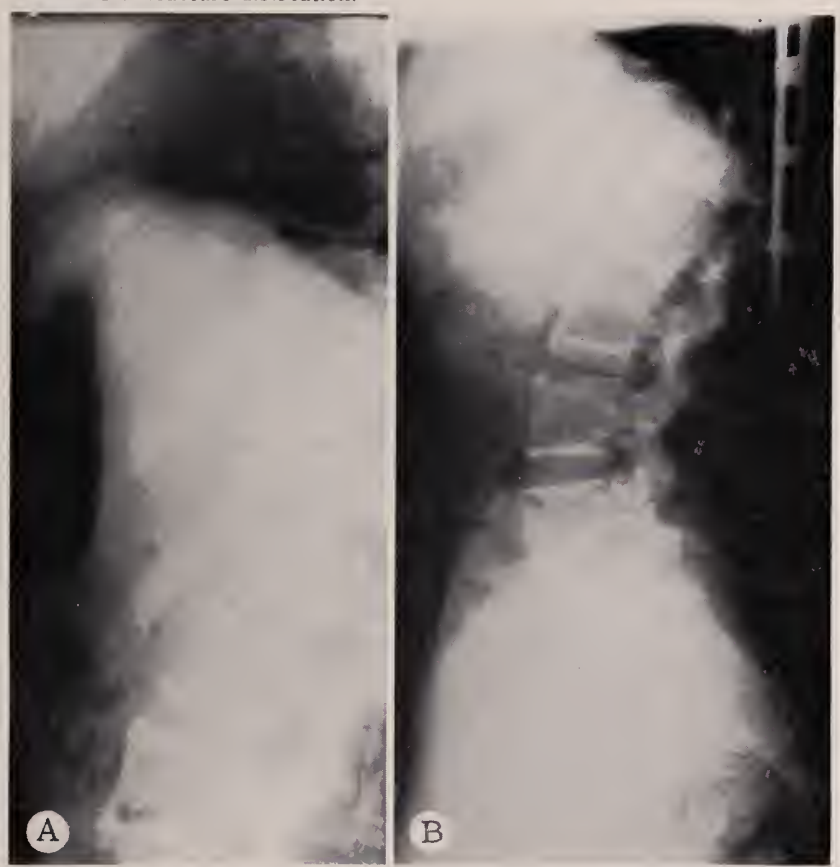


Fig. 3—Lumbodorsal spine of a 19-year-old girl with traumatic paraplegia. (A) Lateral view of fracture of body and lamina of T-12. (B) Lateral view after stabilization of spine with Williams plates.

after anterior poliomyelitis[3] and spinal cord injuries,[4-5] and in part on clinical impressions during rehabilitation of paraplegic and tetraplegic patients of our own.

Effect of Prolonged Immobilization

The development of osteoporosis during prolonged immobilization has been studied in detail in normal subjects[1] and in patients.[3,5] Soon after the second week of immobilization the urinary *excretion of calcium* begins to increase, usually reaching its peak (twice normal value) during the fifth and sixth weeks of immobilization. It then continues at this level, which equals the maximal renal excretory capacity for calcium. Not infrequently, however, mobilization of calcium from bone during prolonged immobilization exceeds the renal excretory capacity. In that event, *hypercalcemia* develops and persists in immobilized patients for one year or longer.[3]

Renal Insufficiency

Renal tubular damage associated with persistent hypercalcemia may lead to hypertension, uremia, and encephalopathy.

The formation of *urinary calculi* is one of the most troublesome complications of ongoing demineralization of bone. Urinary stasis, high concentration of urine due to inadequate fluid intake, and chronic infection of the urinary tract following continuous catheter drainage also seem to be of equal importance for the development of urinary calculi. It is estimated that up to 50% of patients with spinal cord injury eventually die from renal insufficiency with renal calculi present.

Anabolic steroids are capable of stopping mineral loss from bone during immobilization, but their cost and possible side effects limit their use. The ideal management of developing osteoporosis of immobilization in patients with spinal cord injury today appears to be early mobilization. Sitting, standing, and a limited amount of walking with crutches alone, however, do not seem to be very effective in reversing the mineral loss from bone but may slow down the process. For remineralization, substantial muscle work is required.[5] After four weeks of immobilization, normalization of urinary excretion of calcium occurred in healthy young men only after six weeks of strenuous physical reconditioning.[1]

Adequate fluid intake (2,500 to 3,000 ml/day) eliminates high urinary concentration and decreases urinary stasis. It also decreases the incidence of pyelonephritis in patients with spinal cord injury. Intermittent catheterization of the bladder early during the course of traumatic paraplegia has been advocated in recent years[6] as a way to maintain sterility of the bladder. The patient is catheterized four times daily under strict aseptic precautions. If this is started immediately after spinal cord injury, the urinary tract in most patients can be kept sterile, with very few complications arising before bladder training can be started.[7]

Nitrogen Balance

Taylor and colleagues[1] reported that a negative nitrogen balance, as evidence of protein catabolism, became measurable after one week of immobilization. Healthy young men lost an average of 37 gm of nitrogen during four weeks of immobilization. Such nitrogen loss corresponds to the loss of approximately 1 kg of skeletal muscle, not taking into account the possible decrease of other organ tissues. Our clinical impression of immobilized pa-

tients with spinal cord injuries, especially when chronic infection and pain are present, is that rapid deterioration of strength occurs in the unparalyzed muscles. Hettinger[8] suggested an average decrease in muscle strength of approximately 20% per week during complete inactivity over several months.

Cardiovascular Changes

Taylor and colleagues[1] reported that substantial deconditioning of the cardiovascular system developed within four weeks after the start of strict bed rest in previously well-conditioned young men. Heart volume decreased by 17%, and maximal oxygen uptake by 20%. Resting pulse rate increased by about half a beat per day to a total of 14 beats per minute during the four weeks of bed rest. Orthostatic hypotension developed consistently. Approximately four weeks of strenuous physical reconditioning was necessary to normalize heart volume, maximal oxygen uptake, and resting pulse rate, while normalization of orthostatic hypotensive responses took even longer.

Decubitus ulcers usually can be avoided today with effective nursing care. However, when they develop, they generally become the seat of chronic infection and provide another strong impetus to deconditioning of multiple organ systems.

Thrombophlebitis in paralyzed lower extremities develops relatively frequently soon after spinal cord injury. If the circulation is assisted with the use of well-fitted elastic stockings, the incidence of thrombophlebitis decreases substantially.

Myositis ossificans often develops during the period of hypercalcemia—in approximately 30% of patients with paraplegia or tetraplegia. It usually develops about the hips, but also sometimes about the shoulders and knees, and may be related to degeneration of soft tissues under the influence of chronic, repetitive mechanical trauma during prolonged immobilization.

Motor Function

Deterioration of the motor function of the central nervous system has been observed during prolonged immobilization. Taylor and colleagues[1] noted an increase in "sway rate" during standing in their subjects, as well as signs of mild incoordination of upper and lower extremities during prolonged immobilization. The effects of restricted activity on the human body have been reviewed in detail by Kottke.[9]

Emotional Depression

Emotional effects of prolonged periods of immobilization often can be observed in patients with spinal cord injury. During immobilization the patient is forced into substantial dependency on others who care for his feeding, drinking, and emptying of bowel and bladder. He is continually deprived of physical and interpersonal activities on which he had relied for feelings of satisfaction, self-esteem, and happiness prior to immobilization. Dependency, by necessity, becomes more or less the accepted way of operating during prolonged immobilization. In time, emotional gains from dependency on the part of the patient develop. Dependency on such secondary emotional gain often tends to delay the development of normal interpersonal relationships later during rehabilitation.

During prolonged immobilization the patient is also forced to overlook his residual physical work capacity and is prevented from using it. He is continuously confronted with his massive physical loss. Reactions of emotional depression, a basically normal response of grief over his lost function, there-

fore tend to be exaggerated. When early mobilization is possible, for instance following the early stabilization of an unstable vertebral column, the patient's grief reactions tend to be much more realistic, less severe, and of shorter duration, since he is given a chance to learn to appreciate his residual functional capacity much earlier.

Dr. Edward D. Henderson:

My father used to say that the reason orthopedic surgeons have gradually taken trauma away from general surgeons is that the orthopedic surgeon has to deal with rehabilitation and reconstruction of injured and disabled parts. What he was talking about is that in caring for a man with a fractured ankle the orthopedic surgeon is more likely to consider what the subsequent deformity or disability may be and to treat the injury accordingly. I think the same is true in spinal injuries.

A little earlier I was asked whether I used bone grafts with plates. I don't object to bone grafting. I just think that when it seems likely that the bone and ligaments will heal it is not necessary, and bone grafting does prolong the procedure in a patient who already has a severe injury to the spine. I don't know who developed these plates, but one was developed by Meirig Williams of Wales because extensive coal mining in Wales results in many compression fractures with and without spinal cord injury. If you try it and see how it works, I think you will be convinced too. It doesn't really sound logical that one can take a couple of plates that look like miniature railroad tracks, bolt them to the spinous processes, and expect them to immobilize the spine. But they do. I think it is the engineering of the plates that makes them effective. If they are at all painful in later months, as in our third patient, they can be taken out as soon as the spine has fused solidly.

Another important factor is that in prolonged immobilization the dependent portions of the subcutaneous tissue and skin become edematous. If these areas do not have sensation and the patient is moved about and scrapes the skin, pressure or bed sores will develop. Most impressive in the series of cases from which we have presented three this morning is the lack of decubitous ulcers, another reason for early mobilization. I doubt that any of us have to be convinced that prolonged immobilization is to be avoided: a primary consideration in one's approach to the management of spinal cord injuries.

In summary, let me make the following points:

1. Prolonged immobilization, for whatever cause, profoundly affects all physiologic systems.

2. As Dr. Opitz mentioned, these effects are long-lasting and require many months of effort even by healthy people to overcome.

3. Because of his spinal cord injury, the paraplegic or tetraplegic patient suffers even greater loss from immobilization than does a person with a reversible lesion.

4. The use of metal fixation to stabilize the bony spine allows earlier mobilization of the patient with spinal cord injury, thus obviating many of the severe effects of immobilization.

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References may be secured from the author or the reprints.

Clinical Notes

Occult Peau D'orange

An Early Clinical Sign of Breast Cancer

PEAU D'ORANGE, THE pinpoint dimpling in the skin—similar to the skin of an orange—is often seen overlying the lesion in advanced carcinoma of the breast. It is by no means an early clinical sign.

I have been unable to locate a term to describe the sign which I have observed as an early one, but which in all probability eventuates in the obvious peau d'orange. I have therefore chosen to designate this sign as "occult peau d'orange." It can be detected only by gentle pressure at a distant point on the skin, as a small area of pinpoint dimpling of the skin. This is the earliest clinical sign of carcinoma of the breast that I have ever observed. It may occur in advance of an obvious palpable mass, and it is often observed when there is no evidence of calcific stippling as seen in the x-ray mammogram. It is pathognomonic when it is observed, but is sometimes misinterpreted as a minute, localized fold in the skin, because an underlying mass is not readily obvious. It is usually not evident when the breast is dependent.

In many instances this sign is clinically producible before the patient herself has been aware of a mass; and, because the patient rarely consults the physician until she is aware of a mass, it is frequently overlooked, except on routine and careful periodic examinations.

The occult peau d'orange sign is clinically produced by having the patient lie supine on the examining table; the pressure of the patient's arm against the adjacent breast may cause the sign to appear; but when the arm is moved away, the phenomenon disappears; the doctor's hand, at a remote portion of the breast, pressing to displace the breast from its dependent position will cause the small area of pinpoint dimpling to appear over the underlying lesion. Obliquely directed, light, which can produce a shadow at the pinpoint dimples, aids in its detection, whereas a vertical light may eliminate these shadows.

Remote gentle displacement of the breast should be done from all quadrants while watching for the minute dimpling to appear at a distant area. By examining the breast with the flat wet fingers and palm, stroked slowly over the breast and the area of clinical suspicion, a very small underlying lesion can be detected at the site of the occult dimpling. A dry hand cannot be made to pass as smoothly or as softly over a dry skin because it flutters, ever so slightly, and the acute sense of touch is lost.

Carl O. Rice, M.D., Ph.D.

Life

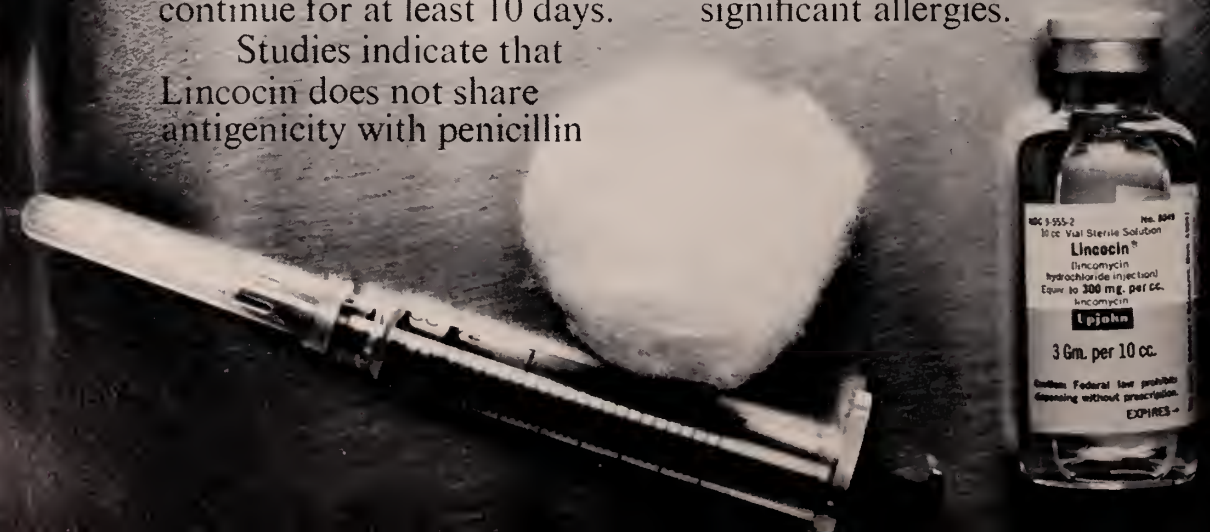
Life is no brief candle to me. It is a sort of splendid torch that I have got hold of for the moment.—George Bernard Shaw

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So is penicillin-resistant staph.

Lincocin (lincomycin hydrochloride, Upjohn) has been demonstrated to be effective in susceptible penicillinase-producing staphylococcal infections resistant to penicillin (including ampicillin). However, resistant staphylococcal strains have been recovered; resistance appears to occur in a slow stepwise manner. As with all antibiotics, susceptibility studies should be performed.

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(lincomycin hydrochloride, Upjohn) for respiratory tract, skin, soft-tissue, and bone infections due to susceptible streptococci, pneumococci, and staphylococci

Each preparation contains:	Lincomycin hydrochloride monohydrate equivalent to lincomycin base
250 mg. Pediatric Capsule	250 mg.
500 mg. Capsule	500 mg.
*Sterile Solution per 1 ml.	300 mg.
Syrup per 5 ml.	250 mg.

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An antibiotic chemically distinct from others available, indicated in infections due to susceptible strains of staphylococci, pneumococci, and streptococci. *In vitro* susceptibility studies should be performed.

CONTRAINDICATIONS: History of prior hypersensitivity to Lincocin (lincomycin hydrochloride). Not indicated in the treatment of viral or minor bacterial infections.

WARNINGS: Cases of severe and persistent diarrhea have been reported and at times drug discontinuance has been necessary. This diarrhea has been occasionally associated with blood and mucus and at times has resulted in acute colitis. This reaction usually has been associated with oral therapy, but occasionally has been reported following parenteral therapy. Although cross sensitivity to other antibiotics has not been demonstrated, make careful inquiry concerning previous allergies or sensitivities to drugs. Safety for use in pregnancy has not been established and Lincocin is not indicated in the newborn. Reduce dose 25 to 30% in patients with severe impairment of renal function.

PRECAUTIONS: Like any drug, Lincocin should be used with caution in patients having a history of asthma or significant allergies. Overgrowth of nonsusceptible organisms, particularly yeasts, may occur and require appropriate measures. Patients with pre-existing monilial infections requiring Lincocin therapy should be given concomitant antimonilial treatment. During prolonged Lincocin therapy, periodic liver function studies and blood counts should be performed. Not recommended (inadequate data) in patients with pre-existing liver disease unless special clinical circumstances indicate. Continue treatment of β-hemolytic streptococci infection for ten days to diminish likelihood of rheumatic fever or glomerulonephritis.

ADVERSE REACTIONS: *Gastrointestinal*—Glossitis, stomatitis, nausea, vomiting. Persistent diarrhea, enterocolitis, and pruritus ani. *Hemopoietic*—Neutropenia, leukopenia, agranulocytosis, and thrombocytopenic purpura have been reported. *Hypersensitivity reactions*—Hypersensitivity reactions such as angioneurotic edema, serum sickness, and anaphylaxis have been reported, sometimes in patients sensitive to penicillin. If allergic reaction occurs, discontinue drug. Have epinephrine, corticosteroids, and antihistamines available for emergency treatment. *Skin and mucous membranes*—Skin rashes, urticaria, vaginitis, and rare instances of exfoliative and vesiculobullous dermatitis have been reported. *Liver*—Although no direct relationship to liver dysfunction is established, jaundice and abnormal liver function tests (particularly serum transaminase) have been observed in a few instances.



Cardiovascular—Instances of hypotension following parenteral administration have been reported, particularly after too rapid I.V. administration. Rare instances of cardiopulmonary arrest have been reported after too rapid I.V. administration. If 4.0 grams or more administered I.V., dilute in 500 ml. of fluid and administer no faster than 100 ml. per hour. *Local reactions*—Excellent local tolerance demonstrated to intramuscularly administered Lincocin. Reports of pain following injection have been infrequent. Intravenous administration of Lincocin in 250 to 500 ml. of 5% glucose in distilled water or normal saline has produced no local irritation or phlebitis.

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Laboratory Letter

Parable of a Punctured Pathologist

Pathology is the accomplished tragedy; Physiology the basis on which the treatment rests.
—Edward Martin, M.D., 1859-1938.

A STUDY just completed on a pathologist demonstrates that his SMA-12/60 results varied little when done on aliquots of one serum sample over a one-week period (Table 1).

TABLE 1
Weekly Quality Control Data on One Pathologist

	Mean	Standard Deviation	Percent Variation
Calcium	9.9	0.1	1.0%
Phosphorus	3.2	0.1	2.4%
Glucose	113	2	1.8%
BUN	15.8	0.4	2.5%
Uric Acid	7.3	0.2	2.7%
Cholesterol	194	6	3.1%
T. Protein	7.5	0.1	1.3%
Albumin	5.0	0.1	2.0%
T. Bilirubin	0.70	0.04	5.7%
Alk. P'tase	27.4	1.1	4.1%
LDH	112	5.5	4.1%
SGOT	38.8	2.7	6.9%

Nor did the results of aliquots of a commercial abnormal sera run daily for 30 consecutive days.

TABLE 2
Monthly Quality Control Data on Known Abnormal Serum

	Mean	Standard Deviation	Percent Variation
Calcium	12.30	0.20	1.6%
Phosphorus	1.80	0.10	2.4%
Glucose	252	4	1.6%
BUN	49.3	0.8	1.6%
Uric Acid	9.5	0.1	1.5%
Cholesterol	148	5	3.4%
T. Protein	5.9	0.1	1.4%
Albumin	3.07	0.06	1.9%
T. Bilirubin	4.7	0.1	2.1%
Alk. P'tase	228	8	3.3%
LDH	350	8	2.3%
SGOT	247	2	0.9%

So far this all sounds grand. Still there are occasions when you receive an SMA-12/60 result you can't explain or don't trust. Yet when you repeat it on another day, the troublesome test is either normal or significantly different than it was the first time.

If the SMA-12/60 differs so little, how do we account for these shifting daily results? Simple. On the basis of changes that occur in the patient. Physiological events —such as eating, drinking, exercising, fasting, or not fasting—can significantly change serum concentrations.

Table 2 shows only minor variations in serum concentrations in the pathologist when one sample of his blood is run again and again for a week. Yet if we take this same pathologist and *draw daily samples after certain physiological events,* the percent physiological variation is two to 10 times as great as the technological variation (Table 3 and Table 4). Note particularly the two right-hand columns in Table 4.

TABLE 3
Daily Changes in SMA-12/60 Chemistries after Physiological Events

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	Fasting; baseline; drawn after 48 hrs. of rest; no alcohol. All tests are normal.	Fasting; drawn 13 hours after 3 ounces of gin and high protein meal; note increase in phosphorus and uric acid.	Fasting; in fact, drawn after 36 hr. fast: note bilirubin and SGOT rise.	Fasting; but drawn 12 hrs. after meal containing 1 pound of roast pork; note BUN and uric acid elevations.	Fasting; 6 hours after drinking 15 ounces of 86 proof scotch; note uric acid elevation and glucose rise.	Non-fasting; 2 hrs. after bacon and eggs; specimen 1 + lipemic; note low phosphorus.	Non-fasting; 2 hrs. after lunch of roast beef, shrimp, and macaroni; serum 1 + lipemic; note low phosphorus.
Calcium	9.9	9.5	9.8	9.6	9.6	9.6	9.4
Phosphorus	3.2	3.6	3.1	3.2	3.4	2.6	2.8
Glucose	113	94	100	89	147*	106	115
BUN	16	19	13	22	15	15	13
Uric Acid	7.3	8.9	7.6	8.5	9.9	7.5	6.5
Cholesterol	194	171	218	185	197	176	184
T. Protein	7.5	6.9	7.4	7.0	7.5	7.0	6.9
Albumin	5.0	4.4	4.9	4.6	5.0	4.5	4.5
T. Bilirubin	0.7	0.7	1.7	0.6	0.6	0.3	0.7
Alk. P'tase	27	27	31	26	29	25	24
LDH	112	105	115	110	104	103	112
SGOT	39	39	53	34	39	37	35

*Because of 147 glucose, three-hour glucose tolerance performed: fasting 106, ½ hour 181, one hour 189, two hour 142, three hour 70. Negative for diabetes.

TABLE 4
Quality Control Data on Daily Serum Samples of Pathologist after Various Physiological Events

	Mean	Standard Deviation	Perce t Variation	Ratio of Physiologic to Technological Variation*
Calcium	9.7	0.15	1.5%	No Change
Phosphorus	3.1	0.4	12.9%	4.0 times
Glucose	108	18	16.7%	9.0 times
BUN	16	3	18.8%	7.5 times
Uric Acid	8.1	1.1	13.7%	5.5 times
Cholesterol	183	16	9.0%	2.7 times
T. Protein	7.1	0.2	2.8%	2.0 times
Albumin	4.80	0.25	5.2%	2.5 times
T. Bilirubin	0.80	0.60	75.0%	15.0 times
Alk. P'tase	27.0	2.5	9.3%	2.3 times
LDH	108	4.5	4.2%	No Change
SGOT	40.0	6.0	15.0%	2.2 times

*What this column says is simply this: that the results on the samples drawn daily varied much more than the results of the sample drawn the first day, then run daily. In short, the person varied more than the SMA-12/60.

Closing Remarks

Why this experiment on a pathologist?

Well, in the first place, he was convenient and easy to control. "The pathologist," as Doctor Holmes remarked, "is useful when kept to heel."*

In a second (and more saphenous) vein, we used him to illustrate these points:

1. Quality control statistics are not just numbers; they are numbers that represent people.
2. *What* people do, *what* they eat, *what* they drink and *when* they do these things influence chemical results more than machine variation.
3. Quality control is a *two-way street*. We can control our side of the street to within ± 1-5%. But results on the patient's side may vary considerably more because of factors beyond our control.

Richard L. Reece, M.D.
Minneapolis, Minnesota

Acknowledgement: I should like to thank Robert Cooper, chief chemist at Lufkin Medical Laboratories, for encouraging me to do this study, and technologists, Mrs. Betty Noseworthy and Mrs. Nancy Naig, for their daily needling.

*Holmes, G.: Arch Intern Med 116:164, 1965.

Neurological Grand Rounds

Anticoagulation in Cerebrovascular Disease

RUSSELL B. BUTLER, M.D.*

Case Report

History

A right-handed 62-year-old man was admitted to the Chisholm, Minnesota, Hospital in October 1968 for acute urinary retention. On the second day of his hospitalization his wife noted that he had an abrupt onset of speech difficulty. Within an hour or two after the episode he had cleared from his symptomatology; however, seven days later he had a sudden onset of coma with a left hemiplegia. From this episode he gradually improved, first regaining consciousness after 10 days, and by five to six weeks he was able to verbalize. At the time of his transfer to the Minneapolis Veterans Hospital he was able to recognize members of his family and was using simple but profane language. His past medical history revealed that he had had a history of hypertension for several years for which he was being treated with Serpasil® (reserpine) and Esidrix® (hydrochlorthiazide). One year prior to his admission he had been placed on Digoxin for symptoms of congestive heart failure and atrial fibrillation.

Physical Findings

Physical examination at the time of his admission revealed an alert, awake man who was unable to communicate verbally except for "Hello" and jargon speech. He was obviously hemiplegic on the left side. His blood pressure was 150/60 mm Hg. His pulse was irregularly irregular at a rate of about 65 per minute. There was a left homonymous hemanopsia. The eyes were deviated to the right. The corneal response was decreased on the left side. There was also a central VII nerve deficit on the left side and he was unable to extend his tongue on command. The sensory examination was gross, but a left hypalgesia was inferred from the facial response. He had bilateral sucking responses, snouting responses and an increased jaw jerk. The reflexes were pathologic bilaterally but were more brisk on the left side. He was unable to cooperate for examination of coordination; however, no abnormal movements were noted. The laboratory data and evaluations were all normal except for the electrocardiogram which showed atrial fibrillation. His cholesterol levels were normal.

This man presents a history compatible with recurrent and bilateral cerebrovascular accidents, probably of an ischemic nature, and a history of atrial fibrillation and congestive heart failure for at least one year, compounded by a history of hypertension for several years.

Anticoagulant Therapy

The question arises whether anticoagulation was indicated in this patient a year ago or when he had his first evidence of cerebrovascular occlusion in October 1968, or whether he would benefit from anticoagulant therapy now.

Ischemic Disease

In 1951 C. Miller Fisher[9] presented one of the first cases of cerebral occlusive disease treated with anticoagulation. In this case the anticoagulant was Heparin. The patient had total occlusion of the internal carotid and did not survive with the treatment. Prior to that time vascular surgeons had often used anticoagulation in combination with sympathetic blockade for the treatment of occlusive vascular disease, outside of the central nervous system.[18]

*Minneapolis Veterans Hospital, Neurology Service, Minneapolis, Minnesota.

In 1955 Millikan[15] recommended that anticoagulation be used in ischemic central nervous system disease and, thereafter, it became quite popular. At that time, use of anticoagulation was, unfortunately, based on rather incomplete and simplified views of clotting mechanisms and of the role of these mechanisms in intravascular coagulation.

Before the benefit of any mode of treatment can be ascertained, it is necessary to describe the disease being treated and its natural history. Though Heparin and Coumadin derivatives have not clearly demonstrated any benefit to the patient in cerebrovascular diseases, they have caused neurologists to look carefully at the frequent afflictions they have been observing.

Basilar Artery Syndrome

In 1962 Williams and Wilson[20] discussed the natural history of the major and minor manifestations of the basilar artery syndromes and concluded that the basilar syndromes were in fact more common than had been appreciated and were even compatible with life. John Marshall[13] presented his article, "The Natural History of Transient Ischemic Attacks," in which he emphasized that there is a difference in the prognosis of ischemic episodes, depending on whether the symptoms involve the carotid or the basilar circulation. It was his point that an attempt to evaluate any treatment must take this difference into consideration. In 1963 Carter[6] discussed the prognosis and the natural history of stroke syndromes.

Occclusive Disease

A national cooperative study conducted with the Veterans Administration and led by R. N. Baker critically evaluated the use of anticoagulation in occlusive disease of the cerebral circulation.[1,2] This study divided occlusive disease into five categories.

Transient Ischemic Attacks

Transient ischemic attacks were defined as a single or multiple episode of cerebral dysfunction, lasting no longer than one hour and without residual defects.

In this group of patients there was a decrease in the number of transient episodes with the use of anticoagulation. However, it was noted that the control group developed less symptomatology with time and that the ultimate prognosis of both groups was the same. It was recommended, therefore, that if anticoagulation were employed, its prolonged use was not warranted.

Thrombosis in Evolution

The patient with thrombosis in evolution was described as having an episode characterized by progressive, step-wise, neurologic loss. The prognosis was so poor that treatment did not seem to make an appreciable difference; however, it was noted that the residual defect in those who survived was less severe in the treated group than in the untreated.

Complete Thrombosis

This was defined as a stable, neurologic complaint with a history of accompanying transient ischemic episodes or other evidences of general vascular thrombotic disease.

The patient who had complete thrombotic episodes responded no differently after treatment than did those who were untreated. Mortality was higher in the treated group when the duration of therapy was taken into consideration.

The most common complication in the treated group was that of hemorrhage into the existing infarct or other areas.

Embolization

The use of anticoagulation in the treatment of embolic disease has been contested not only by neurologists but also by cardiologists and cardiac surgeons.[21] The conclusions of the cooperative study of cerebrovascular disease parallel those of Cooley and others[21]: namely, that there is no definite advantage in the use of anticoagulation in patients with arrhythmia with prostatic valves, or even with cardiac valvular disease. In the central nervous system disease study, the prognosis was the name for groups with or without anticoagulation.

Thorem

Patients with the "Thorem," had an abrupt single neurologic episode where it was impossible to differentiate between embolus and thrombus. They failed to show any definite advantage when treated with anticoagulation.

Comments

It is curious why anticoagulation is not of more benefit in the therapy of occlusive vascular disease within the nervous system. However, the pathology and pathogenesis of the transient ischemic attacks are as yet vague. White bodies have been noted passing through the vessels of the retina during transient amaurosis associated with such episodes.[11] These corpora, it has been suggested, are composed of cholesterol or platelet-fibrin, or of platelet aggregates. In an attempt to evaluate the pathology, material obtained at the time of carotid endarterectomy was examined and bodies of fibrin or platelet aggregates were sometimes found loosely attached to the thrombus. These bodies may persist even with long-term anticoagulation therapy.[21]

Pathology of Infarction

The pathology of the infarcted areas in the brain after embolization led Fisher and Adams[9] in 1951 to propose that the incidence of hemorrhagic infarction may be greatest after the process of embolization. They described several small hemorrhages in the infarcted areas and postulated that diseased vessels could not withstand the systemic blood pressure after the occlusion had been bypassed. This may be why patients who had been on treatment in the aforementioned cooperative study did so poorly after embolization.

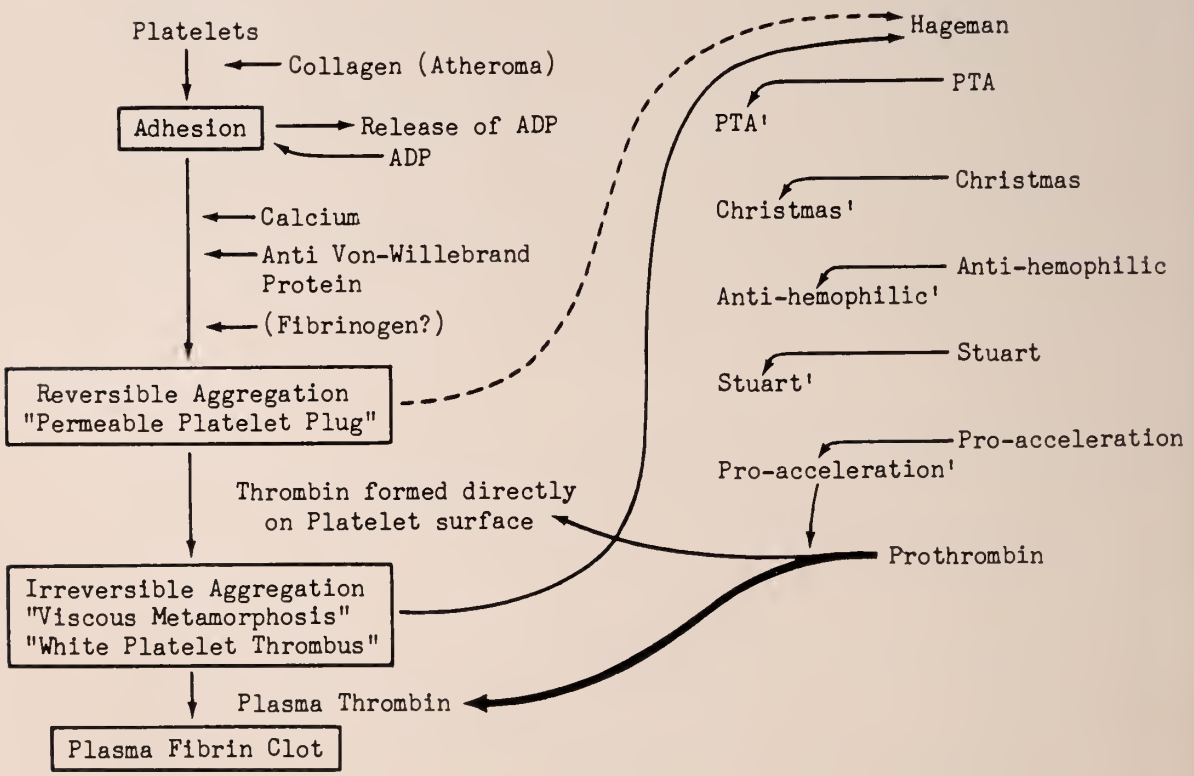
The Effect of Treatment

The failure of treatment had been noted by many observers to be most commonly associated with hypertension or inadequate control of the clotting times.[10,14] However, Baker et al.[4] were unable to demonstrate the significance of hypertension in their study on transient ischemic attacks. In the Cooperative Study,[1,2] prothrombin times were followed as carefully as possible and could be monitored without great difficulty; a question may be raised, however, as to whether control of the symptoms was related to prothrombin time.[17] It has already been stated that some of the pathology in transient ischemic attacks may be due to emboli composed, at least in part, of platelets, which apparently are necessary in the formation of the thrombus. The weakest part of the thrombus may be platelet aggregates which subsequently dislodge and embolize.[7,12,16,17] Treatment with dicoumerol anticoagulants such as Coumadin

or Dicoumeral appears to have no affect on platelet function; therefore, anticoagulants should not have been expected to be of any therapeutic value in cases where platelet emboli are responsible for the symptoms.

Platelets

In vivo, platelets may be stimulated to adhere together by damage occurring in the endothelial walls (Figure). An even stronger influence on the induction of adhesiveness seems to be contact with collagen fibers. With the formation of the adhesive mass of platelets, there is a release of adenosine diphosphate, which, in the presence of calcium and a newly described factor, von Willebrand protein, causes a reversible aggregation of platelets sometimes called a "permeable platelet plug." The von Willebrand plasma protein had been noted to be decreased in von Willebrand's disease, a disorder long suspected of having decreased platelet aggregation. The von Willebrand factor is elevated to abnormal levels in patients with severe atherosclerosis, in diabetes, and in some patients with a familiar hypercholesterolemia. The intrinsic and extrinsic plasma clotting systems are activated in the presence of the previously mentioned substance and thrombin is produced. The thrombin adheres to the platelets and results in an irreversible aggregation of the platelet mass which is called "viscous metamorphosis," or a white platelet thrombus. The reaction may be inhibited by anticoagulates but only in very high dosages. Heparin seems to work the best. The white platelet thrombus stimulates the intrinsic clotting mechanism and plasma thrombin is produced which finally results in a fibrin-platelet mass. With other cellular debris, the fibrin-platelet mass forms a clot of hemostasis.[16]



Figure

Anticoagulation

Anticoagulation had been directed at stages of the intrinsic and extrinsic systems with the use of Heparin to block the activation of Factor IX: (plasma thromoboplastin component: Christmas factor) and antithrombin activity or with the use of Coumadin to decrease thrombin production. Therapy should be directed at platelet aggregation and at the earlier stages of embolus or thrombus formation. The first step in the coagulation sequence may be inhibited by a mono-iodo-acetic acid or British Anti-Lewisite, by anti-histamine, or by cocaine; however, it is stated that very high dosages of these drugs are required to inhibit this process. Dietary control of serum lipids and phospholipids has been suggested, but these techniques have not been fully evaluated at the present time.[16] No safe therapeutic measure to prevent the platelet aggregation is now known; but clearly, anticoagulation using drugs like Coumadin is directed at the process of coagulation too late to be of any benefit.

The patient probably would not have been helped by the use of conventional anticoagulants and they should not have been tried unless he had been symptomatic from the transient ischemic attacks. Perhaps, in a few years, drugs which prevent platelet aggregates may provide a more favorable treatment of recurrent thrombotic episodes not only in the brain but also in the heart.

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A shady business never yields a sunny life.—Forbes Epigrams

On Yawning

by Ashley Montagu

Yawning is a form of behavior which has defied all attempts to explain it.

I don't know whether all mammals yawn, but certainly a large number of them do. All monkeys and apes do so. A trait so widely distributed among mammals and especially in the order to which man belongs, the primates, is likely to be functionally basic or at least to serve some very real organic need.

In man, yawning occurs at all ages and in both sexes. The following are the conditions under which yawning occurs: sleepiness, weariness, on awakening from unrefreshed sleep, and boredom.

All these conditions have in common a lowered state of critical consciousness. "Critical consciousness" here means the state of normal, active awareness of and relatedness to the environment. Any significant decline in critical consciousness may lead to yawning. Reduced critical consciousness is often associated with an increased CO_2 saturation of the blood. Yawning, by its massive inspiration of oxygen and exhalation of CO_2 serves to restore the depleted oxygen content of the blood. The wide opening of the mouth is associated with inspiration of air through the mouth as well as nose, and at the same time by movements of the mandible the branches of the internal and external carotids and the vessels emptying into the jugulars are compressed. Compression probably also occurs of the carotid bodies, all of which contributes to the acceleration of cerebral oxygenation and venous drainage. Virtually all cephalic structures are in consequence stimulated. The excursion of the mandibular condyle upon the prearticular surface of the sphenoid and its return into the mandibular fossa probably produces some encephalic reverberation. All of these changes will tend to contribute to the heightening of consciousness, and this, it is here suggested, constitutes the adaptive value and the principal function of yawning.

It is well known that yawning is contagious, but it would appear to be so principally under conditions of reduced critical consciousness. Thus, the social and biological function of contagious yawning would be to heighten the consciousness of one's fellows by inducing yawning in them in a resulting reciprocally interstimulating situation.

Yawning warns one of the reduction in critical consciousness and, as in sleepiness or weariness, suggests that one ought to sleep or rest or, as in boredom, that one ought to do something about the boredom.*

*Quoted from Berton Roueche: Curiosities of Medicine.

Christmas

Of all the old festivals, that of Christmas awakens the strongest and most heartfelt associations. There is a tone of solemn and sacred feeling that blends with our conviviality, and lifts the spirit to a state of hallowed and elevated enjoyment . . .

*There is something in the very season of the year that gives a charm to the festivity of Christmas. At other times we derive a great portion of our pleasures from the mere beauties of nature . . . But in the depth of winter, when nature lies despoiled of every charm, we turn for our gratification to moral sources . . . We feel more sensibly in the charm of each other's society, and are brought more closely together by dependence on each other for enjoyment.**

*Washington Irving.

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(Continued from page 963.)

schools, we hope to improve the distribution of health care and provide more practicing psysicians for our rural areas.

Other ideas that may be of benefit to improve the health care delivery systems in our rural areas would be Crossroad Clinics, one unit of which would be located in an area where two to three doctors could serve several towns, rather than one physician practicing in each town.

Out-post clinics served by larger clinics are also being encouraged to provide medical care for smaller communities. There must likewise be an increased emphasis on public health and immunization prevention clinics.

The most disturbing aspect of health care of our nation is that aspect over which the nation's physicians have no control. We can strive to improve emergency care, but we cannot prevent the drunken driver from continuing to inflict slaughter on our highways. We can develop new ways of treating cancer of the lung, yet many are not heeding our warning to quit smoking. We can develop coronary care units for the treatment of heart attacks, yet many do not diet and exercise properly to prevent man's number 1 killer. We abhor malnutrition and inadequate housing more than anyone, but still too many of our patients go to bed hungry and wake up with rat bites. It is very difficult for us to solve the problems of poor education, unemployment, superstitions and immorality that all contribute to poor health care. These are just a few of the challenges that the American public must face and to which our Social Service Programs must address themselves. The doctors of America cannot do this alone.

However, the doctors of America should be and are willing to accept the challenge of providing better health care for our patients.

1. We must develop new and innovative methods of treating incurable diseases.
2. We must continue to warn our patients of the pitfalls of too much smoking, too much drinking, too much eating and not enough exercise.
3. We must work with everyone concerned to provide better and more comprehensive health care plans.
4. We must supply as much leadership as we can to provide better housing and more appropriate nutrition.

These are just a few of the areas to which we must direct our energies and our talents. There is no place in this health care arena for the political opportunist or the person with parochial interests. We must strive for many new ideas and repudiate the fear of failure. For as President Nixon stated in June at Atlantic City, "The satisfaction of doing is to develop the capacity to do more."

Robert T. Kelly

President
Minnesota State Medical Association

Characteristics Of The Medical Profession

No other profession can boast of the same unbroken continuity of method and ideals. We may indeed be justly proud of our apostolic succession. Schools and systems have come and gone . . . the philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the vision of tomorrow; through long ages which were slowly learning what we are hurrying to forget—amid all the changes and chances of twenty-five centuries, the profession has never lacked men who have lived up to the Greek ideals.

Of no other profession is the word universal applicable in the same sense . . . It is not the prevalence of disease or the existence everywhere of special groups of men to treat it that betokens this solidarity, but it is the identity throughout the civilized world of our ambitions, our methods, and our work . . . The profession in truth is a sort of guild or brotherhood, any member of which can take up his calling in any part of the world and find brethren whose language and methods and whose aims and ways are identical with his own.*

*Sir William Osler (1849-1920) as quoted in A. C. Corcoran, M.D., A Mirror up to Medicine, 1961.

OLD DOC HESS SAYS: We may have a few problems of ecology in this country, but how would you like to go back to my day and fight the Indians?—C.O.R.

Books Worth Having

1. Advanced Surgical Techniques, an Atlas—*Edward J. Beattie, Jr.* and *Stephens G. Eteonomou.* Publisher: W. B. Saunders Co. Pages—442.

This is an atlas extensively illustrated with wash drawings, covering the field of general surgery. It illustrates principally the basic techniques.

2. Cardiology, A Premier—*George E. Burch.* Publisher: Lea & Febiger. Pages—350.

This is an introduction to cardiology to learn the fundamental principles. An excellent reference.

3. International Handbook of Medical Science—*David Horrobin & Alexander Gunn.* Publisher: G. P. Putnams Sons. Pages—744. Price: $16.00.

For a wide range of medical problems, this book serves as a good reference. The index is not comprehensive, but the page headings are of value in obtaining more specific reference. Under the heading of Common Emergencies the authors describe the acute neck, the acute back, the acute abdomen, acute vomiting and diarrhea, acute poisoning, acute dyspnea, and a number of other acute symptoms. They refreshingly avoid the mention of incidents or injuries as a causative factor, stating further that the physician "should not be too concerned to fit the exact etiological and pathological label, but rather to answer the question 'as to the nature of the individual's illness'."

4. Atlas of General Surgery—*Joseph R. Wilder.* Publisher: C. V. Mosby Co. Pages—325. Price: $23.50.

There are in this atlas 105 surgical procedures illustrated, principally with line drawings. The captions and illustrations are on opposing pages, providing easy reference.

5. Urologic Surgery—*Austin Ingram Dodson, Jr.* Publisher: C. V. Mosby Co. Pages—670. Price: $32.50.

This is a survey of a large volume of urologic diseases, compiled by 13 contributors, all of whom are well qualified in each of their respective interests. For a reference in urology, it is extensive.

6. Practical Urology—*Chester C. Winter.* Publisher: C. V. Mosby Co. Pages—247.

This is a compendium with 251 well chosen illustrations, the majority of which are shown in the x-ray films.

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1. Latiolais, C. J., and Berry, C. C.: Misuse of Prescription Medications by Outpatients, *Drug Intelligence & Clin. Pharm.* 3:270-7, 196

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Ravits, Harold G. ..... St. Paul
Roholt, H. B. ..... Bemidji
Scott, Eugene E. ..... St. Paul
Thayer, Ellsworth A. ..... Fairmont
Van Ryzin, Donald ..... Duluth
Virnig, Richard P. ..... Wells

PERMANENT EVALUATION

Carryer, H. M. (Chairman) ..... Rochester
Blake, Paul S. ..... Minneapolis
Fawcett, K. R. ..... Duluth
Flom, Robert S. ..... St. Paul
Hammar, L. M. ..... Mankato
McCarthy, Donald ..... Minneapolis
Paulson, Elmer ..... St. Paul
Recht, Thomas ..... Minneapolis
Sather, George ..... Fosston
Stoy, Robert A. ..... Little Falls
Wasson, L. F. ..... Alexandria
Wellman, W. E. ..... Rochester
Wells, Walter B. ..... Jackson

PHYSICIANS' ASSISTANCE

Blake, James A. (Chairman) ..... Hopkins
Barr, Lowell ..... Albert Lea
Carlson, Carl E. ..... Alexandria
Coventry, W. D. ..... Duluth
Dobson, M. W. ..... Mankato
Donaldson, C. S. ..... St. Cloud
Engstrom, George ..... St. Peter
Henry, James C. ..... St. Paul
Hoff, Herbert O. ..... Duluth
Holten, John ..... Moorhead
Jenson, James E. ..... Stillwater
Kilbride, E. A. ..... Worthington
Macklin, W. E., Jr. ..... Litchfield
Schmidt, W. Robert ..... Minneapolis
Studer, Donald J. ..... Faribault
Wilmot, Harold E. ..... Litchfield
Younger, Lewis ..... Winona

PROFESSIONAL LIABILITY

Miller, Harold E. ..... Minneapolis
Anderson, Jo E. ..... LeSueur
Brigham, C. F. ..... St. Cloud
Drexler, George W. ..... Blue Earth
Floersch, A. J. ..... Owatonna
Kelly, Edward H. ..... St. Paul
Larson, Gerald ..... Cambridge
Schmid, John ..... Duluth
Wasson, L. F. ..... Alexandria

PUBLIC HEALTH EDUCATION

Sturley, R. F. (Chairman) ..... St. Paul
Executive Committee
Christensen, Norman A. ..... Rochester
Fliehr, Richard R. ..... Minneapolis
Fox, James Rogers ..... Minneapolis
Sturley, R. F. ..... St. Paul
Williams, George ..... St. Paul
Councilor District
Wharton, W. P. (1st) ..... Rochester
Boone, E. S. (2nd) ..... Luverne
Flinn, James B. (3rd) ..... Redwood Falls
Thiem, Chester (4th) ..... Mankato
Williams, George (5th) ..... St. Paul
Semsch, R. D. (6th) ..... Wayzata
Seifert, D. R. (7th) ..... Little Falls
Kuhlmann, V. G. (8th) ..... Alexandria
Jeronimus, Henry J., Jr. (9th) ..... Duluth

PUBLIC HEALTH NURSING

Wilson, Viktor O. (Chairman) ..... Minneapolis
Bosley, Patrick ..... Balaton
Brettingen, L. J. ..... Mora
Fifer, Ellen Z. ..... St. Paul
Guy, Jack A. ..... New London
Houglum, Arvid J. ..... Duluth
Hovde, Gordon ..... Lindstrom
Kitzberger, Peter J., Jr. ..... New Ulm
Knudsen, Helen L. ..... Minneapolis
Koons, Wilbur R. ..... Mahnomen
Mears, B. J. ..... St. Paul
Park, Wilford ..... Minneapolis
Poston, Lawrence ..... Caledonia
Strait, Herbert ..... Minneapolis
Timm, Marvin E. ..... Wabasha

PUBLIC POLICY

Falls, John L., (General Chairman) .....Red Wing
Briggs, Thomas (Vice Chairman) .....White Bear Lake

Councilor District

Spencer, R. J. (1st) .....Rochester
Blumer, Arlo (2nd) .....Albert Lea
Schnell, Frederick (3rd) .....Litchfield
Wohlrabe, Donald (4th) .....Springfield
Sommerdorf, Vernon (5th) .....St. Paul
Benjamin, Robert B. (6th) .....Minneapolis
Fitzsimons, W. E. (7th) .....Brainerd
Wasson, Loren F. (8th) .....Alexandria
Swenson, Arnold O. (9th) .....Duluth

RESIDENTS, INTERNS AND MEDICAL STUDENTS

Wellman, W. E. (Chairman) .....Rochester
Ahmann, David .....Rochester
Andreini, Paul H. .....Rochester
Ballantine, J. J. .....St. Cloud
Baumgartner, C. J., Jr. .....Minneapolis
Blomberg, Robert D. .....Minneapolis
Cavert, H. Mead .....Minneapolis
Duane, Drake .....Rochester
Hakanson, Erick .....St. Paul
Halvorson, James .....Zumbrota
Hay, Lyle J. .....Minneapolis
Hodgson, Stephen .....Rochester
Janssen, Martin E. .....St. Paul
Kane, Dennis .....Minneapolis
Larson, Donald M. .....Duluth
Lewis, F. Bruce .....Minneapolis
McCarthy, Donald .....Minneapolis
Raile, Richard B. .....Minneapolis
Streitz, John M. .....Duluth
Tiede, James .....Rochester

RURAL MEDICAL SERVICE

Berg, A. M. (Chairman) .....Thief River Falls

Councilor District

Gjerde, W. P. (1st) .....Lake City
Odland, Donald M. (2nd) .....LuVerne
Brace, Ray I. (3rd) .....Clinton
Lehrer, A. J. (4th) .....Montgomery
Stratte, A. K. (5th) .....Pine City
Yelle, Matthew D. (6th) .....Anoka
Seifert, Donald R. (7th) .....Little Falls
Berg, A. M. (8th) .....Thief River Falls
Barnes, Richard E. (9th) .....Aurora
Harrison, William C. .....Minneapolis
McCollister, Robert J. .....Minneapolis
Nielsen, David J. .....Minneapolis
Nolen, William A. .....Litchfield
Ringhofer, Lawrence .....New Ulm
Verby, John, Jr. .....Minneapolis

SCHOLARSHIP & LOANS

Bartholomew, L. G. (Chairman) .....Rochester
Alden, John E. .....St. Paul
Christenson, Carl E. .....New Brighton
Engwall, Richard .....Minnetonka
Fritsche, T. R. .....New Ulm
Puumala, R. H. .....Cloquet
Rutledge, John B. .....Detroit Lakes
Sheppard, C. G. .....St. Peter
Spencer, B. J. .....Minneapolis
Verby, John, Jr. .....Minneapolis

STATE HEALTH RELATIONS

Earl, John R. (Chairman) .....St. Paul
Batdorf, B. Niles .....Mankato
Bouquet, B. J. .....Wabasha
Coe, John I. .....Minneapolis
Grose, Frederick N. .....Clarissa
Kilbride, E. A. .....Worthington
Litman, S. N. .....Duluth
Mears, B. J. .....St. Paul
Tesch, Gordon .....Elk River
Thienes, R. L. .....St. Cloud
Votel, Thomas W. .....St. Paul
Wilson, Viktor .....Minneapolis

UNIVERSITY RELATIONS

Nelson, O. L. N. (Chairman) .....Minneapolis
Alexander, Paul .....Hibbing
Buckley, R. P. .....Duluth
Cavert, H. Mead .....Minneapolis
Gillespie, D. R. .....St. Paul
Koop, Severin H., Jr. .....St. Cloud
Monahan, R. H. .....St. Paul
Plasha, Matthew .....Coon Rapids
Spencer, Bernard .....Minneapolis
Stickney, J. M. .....Rochester
Verby, John E. .....Minneapolis
Yonehiro, Earl .....Minneapolis

Councilor Districts

FIRST DISTRICT

G. R. Diessner, M.D. .....Rochester
Counties—Dodge, Fillmore, Goodhue, Houston, Mower, Olmsted, Rice, Steele, Wabasha, Winona.

SECOND DISTRICT

Mark P. Virnig, M.D. .....Wells
Counties—Cottonwood, Faribault, Freeborn, Jackson, Martin, Murray, Nobles, Pipestone, Rock, Watonwan.

THIRD DISTRICT

Williams A. Owens, M.D. .....Montevideo
Counties—Big Stone, Chippewa, Kandiyohi, Lac Qui Parle, Lincoln, Lyon, Meeker, Pope, Redwood, Renville, Stevens, Swift, Traverse, Yellow Medicine.

FOURTH DISTRICT

Wallace E. Mathews, M.D. .....Mankato
Counties—Blue Earth, Brown, Carver, Le Sueur, McLeod, Nicollet, Scott, Sibley, Waseca.

FIFTH DISTRICT

Barnard Hall, M.D. .....St. Paul
Counties—Anoka, Chisago, Dakota, Isanti, Kanabec, Mille Lacs, Pine, Ramsey, Sherburne, Washington.

SIXTH DISTRICT

Richard Frey, M.D. .....Minneapolis
Counties—Hennepin, Wright.

SEVENTH DISTRICT

Florian H. Baumgartner, M.D. .....Albany
Counties—Aitkin, Beltrami, Benton, Cass, Clearwater, Crow Wing, Hubbard, Lake of the Woods, Morrison, Stearns, Todd, Wadena.

EIGHTH DISTRICT

L. F. Wasson, M.D. .....Alexandria
Counties—Becker, Clay, Douglas, Grant, Kittson, Mahnomen, Marshall, Norman, Otter Tail, Pennington, Polk, Red Lake, Roseau, Wilkin.

NINTH DISTRICT

John H. Peterson, M.D. .....Duluth
Counties—Carlton, Cook, Itasca, Koochiching, Lake, St. Louis.

(Dr. R. O. Bergan will replace Dr. Peterson on Jan. 1, 1972)

COUNTY MEDICAL ADVISORY COMMITTEES
To County Welfare Boards

AITKIN COUNTY
George Pettersen ..... Aitkin
F. C. Closuit ..... Aitkin

ANOKA COUNTY
R. J. Spurzem ..... Anoka

BECKER COUNTY
E. S. Lorentzen ..... Detroit Lakes
A. S. Midthune ..... Lake Park

BELTRAMI COUNTY
Howard C. Reid ..... Bemidji
H. A. Palmer ..... Blackduck

BIG STONE COUNTY
Jacob F. Karn ..... Ortonville
Ray I. Brace ..... Clinton
Russell Popoff ..... Graceville

BLUE EARTH COUNTY
C. E. Thiem ..... Mankato
J. R. Sebald ..... Mankato
J. C. Norris ..... Mankato

BROWN COUNTY
Milton Kaiser ..... New Ulm
L. Ringhofer ..... New Ulm
D. E. Wohlrabe ..... Springfield

CARLTON COUNTY
R. H. Puumala ..... Cloquet
Alvan Sach-Rowitz ..... Moose Lake

CARVER COUNTY
R. D. Pistulka ..... Chaska

CASS COUNTY
C. R. Pelzl ..... Pine River
Carl H. Coombs ..... Cass Lake

CHIPPEWA COUNTY
H. A. Roust ..... Montevideo
T. G. Birkey ..... Montevideo

CHISAGO COUNTY
G. W. Hovde ..... Chisago City

CLAY COUNTY
R. A. Colliton ..... Moorhead
V. J. Carlson ..... Moorhead

CLEARWATER COUNTY
L. J. Larson ..... Bagley

COOK COUNTY
Roger R. MacDonald ..... Grand Marais
Wallace R. Smith ..... Grand Marais

COTTONWOOD COUNTY
H. C. Stratte ..... Windom
J. H. Dokken ..... Windom
J. V. Carlson ..... Westbrook

CROW WING COUNTY
Albertus Dodson ..... Brainerd
J. B. Nixon ..... Crosby
Robert Poppie ..... Brainerd

DAKOTA COUNTY
Norbert Kulzer ..... Hastings
James L. Canine ..... So. St. Paul

DODGE COUNTY
D. E. Affeldt ..... Kasson
Grant E. Olson ..... West Concord

DOUGLAS COUNTY
E. J. Tanquist, Sr. ..... Alexandria
Peter M. Geiser ..... Alexandria
J. H. Cain ..... Alexandria

FARIBAULT COUNTY
John W. Anderson ..... Blue Earth
J. A. Watkins ..... Wells
R. S. Armstrong ..... Winnebago

FILLMORE COUNTY
J. E. Westrup ..... Lanesboro
Ralph B. Johnson ..... Lanesboro

FREEBORN COUNTY
L. E. Steiner ..... Albert Lea
Harold Halvorson ..... Albert Lea
H. B. Neel ..... Albert Lea
L. W. Barr ..... Albert Lea

GOODHUE COUNTY
G. F. Hartnagel ..... Red Wing
G. M. B. Hawley ..... Red Wing

GRANT COUNTY
V. A. Doms ..... Elbow Lake

HENNEPIN COUNTY
Mark C. L. Hanson ..... Minneapolis
Charles A. Haberle ..... Minneapolis
Sidney S. Scherling ..... Minneapolis
Nathan C. Plimpton ..... Minneapolis
Lester W. Carlander ..... Minneapolis
George W. Janda, Jr. ..... Minneapolis
Donald B. Frane ..... Minneapolis
Harold E. Miller (Ex-officio) ..... Minneapolis

HOUSTON COUNTY
Hildegard J. Virnig ..... Caledonia
Philip Utz ..... LaCrosse, WI
L. A. Knutson ..... Spring Grove

HUBBARD COUNTY
Howard Mortenson ..... Menahga
Edgar R. Gamm ..... Park Rapids

ISANTI COUNTY
R. C. Magnuson ..... Cambridge

ITASCA COUNTY
Keith H. Stolen ..... Grand Rapids
Robert P. Balderson ..... Grand Rapids
Donald Mueller ..... Grand Rapids

JACKSON COUNTY
V. W. Doman ..... Lakefield
H. A. Christensen ..... Jackson
W. B. Wells ..... Jackson

KANABEC COUNTY
E. C. Burseth ..... Mora

KANDIYOHI COUNTY
Dale Eichelberger ..... Willmar
John Docksey ..... Willmar
Jack Guy ..... New London

KITTSON COUNTY
Roland Larter ..... Hallock

KOOCHICHING COUNTY
George M. Crow ..... International Falls
Frederick H. Walter ..... International Falls

LAC QUI PARLE COUNTY
Chester A. Anderson ..... Madison
V. M. Johnson ..... Dawson

LAKE COUNTY
G. E. Church ..... Two Harbors
Donald Haase ..... Silver Bay

LAKE-OF-THE-WOODS COUNTY
Allen G. Janecky ..... Baudette

LE SUEUR COUNTY
J. E. Anderson ..... Le Sueur

LINCOLN COUNTY
Richard Mulder ..... Ivanhoe
C. Percy Johnson ..... Tyler

LYON COUNTY
K. A. Peterson ..... Marshall
W. M. Kaczrowski ..... Marshall

MAHNOMEN COUNTY
Charles B. Mercil ..... Mahnomen

MARSHALL COUNTY
E. Pumala ..... Warren

MARTIN COUNTY
George N. Kraemer ..... Fairmont
H. A. Williamson ..... Fairmont

McLEOD COUNTY
Clark Truesdale ..... Glencoe
Robert Hegrenes ..... Hutchinson
John J. Smyth ..... Lester Prairie

MEEKER COUNTY
Fredrick S. Schnell ..... Litchfield
G. Olson ..... Litchfield
Joseph C. Houts ..... Dassel

MILLE LACS COUNTY
N. B. Metcalf ..... Princeton

MORRISON COUNTY
S. W. Watson ..... Little Falls
Milo Hansen ..... Little Falls
R. J. Stein ..... Pierz

MOWER COUNTY
Harold J. Anderson ..... Austin
T. M. Seery ..... Austin
H. Miller ..... Austin
Clifford Pesonen ..... Austin

MURRAY COUNTY
R. F. Pierson ..... Slayton
J. L. Bader ..... Slayton
H. D. Patterson ..... Slayton
Dean Nywall ..... Slayton

NICOLLET COUNTY
Vern Olmanson ..... St. Peter
C. Wohlrabe ..... No. Mankato

NOBLES COUNTY
M. W. Plucker ..... Worthington
B. C. Faul ..... Worthington
D. J. Halpern ..... Brewster

NORMAN COUNTY
B. Kinkade ..... Ada

OLMSTED COUNTY
David Carr ..... Rochester
James Doyle ..... Rochester
T. O. Wellner ..... Rochester
T. T. Myers ..... Rochester
Richard Steinhilber ..... Rochester
D. Thurber ..... Rochester

OTTER TAIL COUNTY
Roy Nelson ..... Fergus Falls
Homer Carlson ..... Pelican Rapids
C. W. Lewis ..... Henning
L. Syverson ..... Fergus Falls

PENNINGTON COUNTY
George Martin ..... Thief River Falls

PINE COUNTY
F. M. Mach ..... Pine City

PIPESTONE COUNTY
W. G. Benjamin ..... Pipestone
J. G. Lohmann ..... Pipestone
G. Beckering ..... Edgerton

POLK COUNTY
Howard Wikoff ..... Crookston

POPE COUNTY
Gordon E. Lee ..... Glenwood
Berton A. Kolp ..... Glenwood
Foster D. Bucher ..... Starbuck

RAMSEY COUNTY
Eugene E. Scott ..... St. Paul
Donald B. Swenson ..... St. Paul
John F. Perry, Jr. ..... St. Paul
Charles W. Hauser ..... St. Paul
William J. Lick ..... St. Paul
Frank W. Quattlebaum ..... St. Paul
Charles J. Mishek ..... St. Paul
James O. Wall ..... St. Paul

RED LAKE COUNTY
David Mersy ..... Red Lake Falls

REDWOOD COUNTY
James B. Flinn ..... Redwood Falls
G. W. Kaminski ..... Redwood Falls
G. E. Nelson ..... Redwood Falls

COUNTY MEDICAL ADVISORY COMMITTEES

RENVILLE COUNTY
C. A. Anderson ..... Hector
Leo Furr ..... Bird Island

RICE COUNTY
Roy H. Good ..... Northfield
Asa Graham ..... Faribault
Burton A. Orr ..... Faribault
J. Gordon Beaton ..... Northfield

ROCK COUNTY
Darrel Siebert ..... Luverne
F. W. Bofenkamp ..... Luverne
D. M. Odland ..... Luverne

ROSEAU COUNTY
Jack Delmore ..... Roseau

ST. LOUIS COUNTY
Karl Johnson ..... Duluth
R. P. Buckley ..... Duluth
W. H. Grohs ..... Duluth
J. P. Knoedler ..... Duluth
R. J. Thurn ..... Duluth
Bayard T. French ..... Hibbing
Raymond Martinson ..... Virginia
Anthony Baraga ..... Hibbing
Charles Tietz ..... Virginia
Kenneth E. Ahola ..... Hibbing

SCOTT COUNTY
P. J. Adams ..... Shakopee

SHERBURNE COUNTY
G. H. Tesch ..... Elk River

SIBLEY COUNTY
A. F. Dysterheft ..... Gaylord
J. E. Schroeppel ..... Winthrop

STEARNS-BENTON COUNTY
J. N. Olinger ..... St. Cloud
C. D. Stiles ..... Foley
A. D. Espelien ..... Cold Spring
R. J. Salk ..... St. Cloud
G. K. Kvistberg ..... St. Cloud
L. Stahn ..... St. Cloud
B. L. John ..... St. Cloud
W. H. Rice ..... St. Cloud

STEELE COUNTY
A. J. Floersch ..... Owatonna
T. W. Stransky ..... Owatonna
R. W. deWerd ..... Owatonna

STEVENS COUNTY
R. A. Rossberg ..... Morris
O. A. Eide ..... Hancock
Robert Watson ..... Morris

SWIFT COUNTY
Edward Kaufman ..... Appleton
N. Wagner ..... Benson
T. S. Eberley ..... Benson

TODD COUNTY
Alvin Erickson ..... Long Prairie
F. N. Grose ..... Clarissa

TRAVERSE COUNTY
H. C. Winge ..... Wheaton

WABASHA COUNTY
Gary Feigal ..... Lake City
B. J. Bouquet ..... Wabasha
D. W. Sontag ..... Lake City

WADENA COUNTY
Leland Reichelt ..... Wadena
W. E. Parker ..... Sebeka
W. B. Halme ..... Wadena

WASECA COUNTY
Patrick Hergott ..... Waseca
Raymond C. Hottinger ..... Janesville

WASHINGTON COUNTY
James E. Jenson ..... Stillwater

WATONWAN COUNTY
R. A. Parsons ..... St. James
Herbert Boysen ..... Madelia

WILKIN COUNTY
L. O'Brien ..... Breckenridge
C. W. Jacobson ..... Breckenridge
Neil Kippen ..... Breckenridge

WINONA COUNTY
Herbert vR. Heise ..... Winona
Robert B. Tweedy ..... Winona
Henry J. Roemer ..... Winona

WRIGHT COUNTY
Lester Bendix ..... Annandale
Pierre J. Guilfoile ..... Delano

YELLOW MEDICINE COUNTY
C. L. Lundell ..... Granite Falls
P. G. Schmidt ..... Granite Falls

Woman's Auxiliary to the Minnesota State Medical Association

Officers

Mrs. Howard Andersen	President	Rochester
Mrs. E. S. Boone	President-elect	Luverne
Mrs. Richard Horns	First Vice President	Edina
Mrs. James Tetlie	Second Vice President	Duluth
Mrs. Chauncey Kelsey	Third Vice President	St. Paul
Mrs. Robert Kelly	Fourth Vice President	Grand Rapids
Mrs. John Beuning	Recording Secretary	St. Cloud
Mrs. N. G. Hepper	Corresponding Secretary	Rochester
Mrs. Gerald Larson	Treasurer	Cambridge
Mrs. Theodore Smith	Auditor	Minneapolis
Mrs. James Blake	Historian	Hopkins
Mrs. G. R. Diessner	Parliamentarian	Rochester

Regional Advisors

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Mrs. E. C. Menefee	Second District	Albert Lea
Mrs. James Flinn	Third District	Redwood Falls
Mrs. Olaf Lukk	Fourth District	Prior Lake
Mrs. John B. Brainard	Fifth District	St. Paul
Mrs. Conrad Holmberg	Sixth District	Excelsior
Mrs. L. L. Bissinger	Seventh District	Brainerd
Mrs. Leong Hom	Eighth District	Fergus Falls
Mrs. William Goodnow	Ninth District	Duluth

Chairmen of Committees

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Program—Mrs. E. S. Boone ..... Luverne

Publications: (Gopher Doctor's Wife, Press and Roster)—Mrs. Clarence Rowe ..... St. Paul

By-Laws—Mrs. L. L. Bissinger ..... Brainerd

Finance—Mrs. Cyril R. Tifft ..... St. Paul

In Memoriam—Mrs. W. A. Merritt ..... Rochester

Resolutions—Mrs. J. B. McBean ..... Rochester

CHAIRMEN OF PROGRAM EXTENSION COMMITTEES

AMA-ERF—Mrs. M. I. Shelander ..... St. Paul

Community Health—Mrs. W. G. Halverson ..... Madelia

Mental Health—Mrs. Daniel Cortez ..... Minneapolis

Pre-School Medical Survey of Vision and Hearing—Mrs. Gerald A. Gretsch .... North Oaks

Safety-Disaster Preparedness—
Mrs. Edgar Burseth ..... Mora
Mrs. Gordon Hovde ..... Chisago City

Health Careers—Mrs. Ellery James ..... Mahtomedi

International Health Activities—
Mrs. James Tetlie ..... Duluth

Legislation—Mrs. Robert F. Fischer ..... St. Paul
Mrs. David B. Auran ..... St. Paul

MINNPAC Liaison—Mrs. Robert F. Fischer ..... St. Paul
Mrs. David B. Auran ..... St. Paul

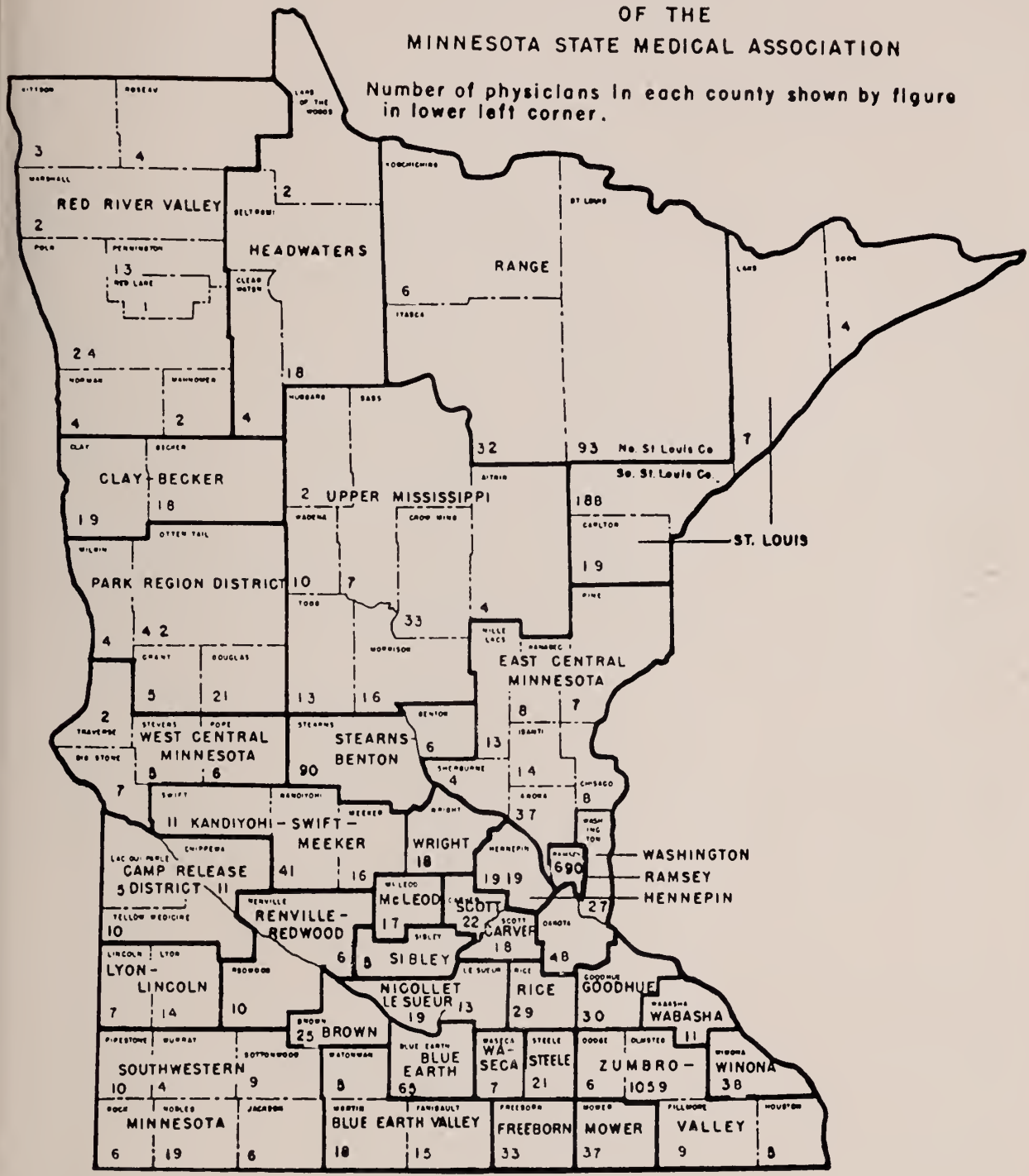
WA/SAMA Liaison—Mrs. John Nilsen ..... Minneapolis

1972 Convention Chairmen:
Mrs. Philip E. Bernatz ..... Rochester
Mrs. James A. Bastron ..... Rochester

Advisory Committee—
Mrs. Cyril R. Tifft ..... St. Paul
Mrs. W. A. Merritt ..... Rochester
Mrs. Josiah Fuller ..... Duluth
Mrs. F. G. Gunlaugson ..... Minneapolis
Mrs. M. I. Hauge ..... Marcell

COUNTY MEDICAL SOCIETIES
OF THE
MINNESOTA STATE MEDICAL ASSOCIATION

Number of physicians in each county shown by figure in lower left corner.



County Medical Society Roster

KEY TO SYMBOLS AS FOLLOWS
* Deceased
† Affiliated, Associated, Life, or Resident Members
Service
‡ Wife is Member of Women's Auxiliary
¶ Honrary Member

BLUE EARTH COUNTY MEDICAL SOCIETY

Blue Earth County
Regular meetings, last Monday of the month
Annual meeting, December
Number of members 61

PRESIDENT
Dobson, M. W. ..... Mankato

SECRETARY
Knowles, William D. ..... Mankato

‡ Anderson, Oscar D. ..... Mankato
‡ Arnesen, Paul M. ..... Mankato
‡ Barbarisi, Charles F. ..... Mankato
‡ Batdorf, B. Niles ..... Mankato
‡ Brady, Charles H. ..... Mankato
† Butzer, John A. ..... Mankato
Cadbury, Jane B. ..... Mankato
‡ Chalgren, William S. ..... Mankato
‡ Conley, Robert H. ..... Mankato
Dobson, Mervin W. ..... Mankato
Eckert, Joseph F. ..... Mankato
Eisenbeis, Charles F. ..... Mankato
Eggert, Delmer C. ..... Mankato
‡ Elliott, J. W. ..... Mankato
‡ Engstrom, Robert B. ..... Mankato
‡ Eustermann, John J. ..... Mankato
‡ Florine, Martin C. ..... Madison Lake
‡ Fortier, R. G. ..... Mankato
† Franchere, Frederick W. ..... Lake Crystal
Freeman, Donald H. ..... Mankato
‡ Geurs, Benjamin R. ..... Mankato
‡ Gislason, Paul H. ..... Mankato
‡ Grande, David W. ..... Mankato
‡ Hammar, Lawrence M. ..... Mankato
Hankerson, Robert G. ..... Mankato
‡ Heimark, John J. ..... Mankato
‡ Heller, Edgar E. ..... Mankato
† Hoeper, Philip G. ..... Chestnut Hill, MA
Huffington, Herb L. ..... Waterville
† Huffington, Herbert L. ..... Brownsville, Texas
†‡ Jones, Orville H. ..... Mankato
‡ Kearney, R. Wynn ..... Mankato
† Kemp, Alphonse F. ..... Mankato
‡ Knowles, William D. ..... Mankato
Langsjoen, Ralph ..... No. Mankato
Lester, John W. ..... Mapleton
‡ Lindblom, Alton E. ..... Mankato
† Luck, Hilda ..... Mankato
‡ Lund, J. Benjamin ..... Mankato
McBride, Alexander M. ..... Mankato
‡ Marso, John L. ..... Mankato
‡ Mathews, Wallace E. ..... Mankato
‡ Meredith, Donald C. ..... Mankato
Mickelson, John C. ..... Los Angeles, CA
Morgan, Hugh O. ..... Amboy
Norris, John C. ..... Mankato
‡ Penn, George F. ..... Mankato
Pope, David A. ..... Janesville
‡ Roth, Frederick D. ..... Mankato
Rozeboom, P. T. ..... Mankato
‡ Sanford, Raymond A. ..... Mankato
‡ Schmitz, Anthony A. ..... Mankato
Sebald, John R. ..... Mankato
‡ Setzer, Hobert J., Jr. ..... Mankato
‡ Sjoding, J. Donald ..... Mankato
‡ Smith, Harry J. ..... Lake Crystal
Snider, Howard R. ..... Mankato
† Stillwell, Walter C. ..... Mankato
Strobel, Claire J. A. ..... Mankato
‡ Swenson, Donald B. ..... Mankato
‡ Thiem, Chester E. ..... Mankato
† Troost, H. Bradley ..... Mankato
† Vezina, John C. ..... Mapleton
‡ Von Drasek, Joseph ..... Mankato
† Wentworth, Albert J. ..... Mankato

BLUE EARTH VALLEY MEDICAL SOCIETY

Martin, Watonwan and Faribault Counties
Regular meetings, third Wednesday of each month
Annual meeting in November
Number of members 37

PRESIDENT
Watkins, J. A. ..... Wells

SECRETARY
Boysen, Herbert ..... Madelia

‡ Anderson, John W. ..... Blue Earth
‡ Armstrong, Ralph S. ..... Winnebago
‡ Bellomo, John ..... Fairmont
†‡ Boysen, Herbert ..... Madelia
*† Bratrude, Earl J. ..... Hopkins
Cox, Russell L. ..... Estherville, IA
Cullen, Robert M. ..... So. Africa
‡ Drexler, George W. ..... Blue Earth
‡ Feigal, William M. ..... Fairmont
‡ Gardner, Jack K. ..... Fairmont
† Gardner, Victor H. ..... Fairmont
‡ Halverson, William G. ..... Madelia
‡ Hanson, Lewis ..... Frost
Hruza, William J. ..... Sioux Falls, SD
‡ Kraemer, George N. ..... Fairmont
‡ Krause, Carl W. ..... Fairmont
‡ Lester, Malcolm J., Jr. ..... Truman
‡ Lindahl, Merlyn J. ..... Sherburn
‡ Mijares, Wilfredo ..... Fairmont
† Mills, John L. ..... Winnebago
‡ Moulton, Keith B. ..... St. James
‡ Nickerson, Neil D. ..... Fairmont
‡ Parsons, R. A. ..... St. James
Parsons, Ralph L. ..... Trimont

Blue Earth Valley Medical Society *(Continued)*

‡ Pitcher, Arlo L. .....St. James
‡ Russ, Homer H. .....Blue Earth
‡ Schotzko, John R. .....Blue Earth
Schulz, Robert W. .....Fairmont
‡ Tempel, J. W. .....Blue Earth
‡ Smith, Don V. .....Blue Earth
‡ Thayer, Ellsworth A. .....Fairmont
‡ Virnig, Mark P. .....Wells
‡ Virnig, Richard P. .....Wells
‡ Wandke, Otto E. .....Fairmont
‡ Watkins, John A. .....Wells
‡ Williamson, Harold A. .....Fairmont
‡ Zemke, Erhart E. .....Fairmont
‡ Zemke, Robert L. .....Fairmont

BROWN COUNTY MEDICAL SOCIETY

Brown County
Regular meetings, second Tuesday
January, April, July and October
Annual meeting in January
Number of members 27

PRESIDENT
Fritsche, Carl .....New Ulm

SECRETARY
Ringhofer, Lawrence .....New Ulm

‡ Black, William A. .....New Ulm
‡ Boyle, Francis J. .....Springfield
‡ Burnett, Joseph W. .....New Ulm
‡ Cairns, Robert J. .....Redwood Falls
‡ Carthey, Frank J. .....New Ulm
Fesenmaier, Otto B. .....Pasadena, CA
† Fritsche, Albert .....New Ulm
‡ Fritsche, Carl J. .....New Ulm
‡ Fritsche, Theodore R. .....New Ulm
Gilles, Thomas F. .....Fairfax
† Goblirsch, Andrew P. .....Sleepy Eye
‡ Johnson, Rex R. .....New Ulm
‡ Kaiser, Milton L. .....New Ulm
‡ Keithahn, Elmer E. .....Sleepy Eye
‡ Kitzberger, Peter J. .....New Ulm
Muesing, William J. .....New Ulm
† Nuessle, Walter G. .....Springfield
‡ Penk, Engward L. .....Springfield
† Peterson, Roy A. .....Vesta
‡ Rimas, Mathew J. .....Comfrey
Ringhofer, Lawrence .....New Ulm
‡ Saffert, Cornelius A. .....New Ulm
Vogel, Ann G. .....New Ulm
Vogel, Howard A. L. .....New Ulm
Wing, Elton G. .....Sleepy Eye
Wohlrabe, Donald E. .....Springfield
‡ Wohlrabe, Edwin J. .....Springfield

CAMP RELEASE DISTRICT MEDICAL SOCIETY

Chippewa, Lac qui Parle and Yellow Medicine Counties
Regular meetings, second Thursday of each month
except July and August
Annual meeting, January
Number of members 24

PRESIDENT
Camp, Ray J. .....Madison

SECRETARY
Westby, Norval M. .....Madison

‡ Allen, John H. .....Montevideo
‡ Anderson, Chester A. .....Madison
‡ Birkey, Thomas G. .....Montevideo
‡ Boody, George J. .....Cambridge
Borgerson, M. A. .....Hanley Falls
Burns, Floyd M. .....Milan
‡ Camp, Ray J. .....Madison
‡ Carter, Kenneth R. .....Granite Falls
Gustafson, Robert W. .....Granite Falls
‡ Hagberg, Norman L. .....Montevideo
†‡ Hauge, Malvin I. .....Marcell
‡ Johnson, Vilhelm M. .....Dawson
† Jordan, Kathleen B. Smith .....Granite Falls
†‡ Kaufman, William C. .....Appleton
‡ Kremer, Jerome L. .....Montevideo
‡ Lima, Ludvig R. .....Montevideo
‡ Lundell, Carl L. .....Granite Falls
‡ Maus, Philip W. .....Dawson
‡ Niazi, Suad A. .....Granite Falls
Owens, William A. .....Montevideo
‡ Radke, Robert L. .....Milan
Rifat, Baseem .....Clarkfield
Roust, Henry A. .....Montevideo
‡ Schmidt, Paul G. .....Granite Falls
‡ Westby, Norval M. .....Madison

CLAY-BECKER COUNTY MEDICAL SOCIETY

Clay and Becker Counties
Regular meeting date, April
Annual meeting, December
Number of members 30

PRESIDENT
Rice, H. G. ..... Moorhead

SECRETARY
Saxman, Gertrude O. ..... Ulen

Bigler, Earl E. ..... Perham
Bigler, Ivan E. ..... Perham
‡ Bologna, Camillo V. ..... Moorhead
† Bottolfson, B. T. ..... Moorhead
Brenk, Paul E. ..... Detroit Lakes
Broadhurst, Kennon E. ..... Detroit Lakes
‡ Carlon, Donald L. ..... Moorhead
‡ Carlson, Vernon J. ..... Moorhead
‡ Colliton, Patrick A. ..... Moorhead
‡ Covey, Kenneth W. ..... Moorhead
Dodds, William C. ..... Detroit Lakes
‡ Duncan, James W. ..... Moorhead
‡ Geib, Marvin J. ..... Fargo, ND
‡ Holten, John ..... Moorhead
† Johnson, Olga H. ..... Moorhead
Knapp, James F. ..... Detroit Lakes
Koons, William R. ..... Mahnomen
Lorentzen, Ernest S. ..... Detroit Lakes
Midthune, Andreen S. ..... Lake Park
Nakamura, James Y. ..... Detroit Lakes
Norberg, William J. ..... Lake Park
Odland, Mark E. ..... Detroit Lakes
‡ Rice, Hagbart G. ..... Moorhead
Rutledge, John B. ..... Detroit Lakes
† Rutledge, Lloyd H. ..... Detroit Lakes
Saxman, Gertrude O. ..... Ulen
‡ Simison, Carl ..... Barnesville
‡ Thysell, Vernon D. ..... Moorhead
Watson, Robert N. ..... Detroit Lakes
Watson, Virgil A. ..... Detroit Lakes

EAST CENTRAL MINNESOTA MEDICAL SOCIETY

Anoka, Chisago, Isanti, Kanabec, Mille Lacs,
Pine and Sherburne Counties
Regular meetings first Tuesday of even
months of the year
Annual meeting, first Tuesday in December
Number of members 41

PRESIDENT
Travis, Richard C. ..... Elk River

SECRETARY
Seecamp, Carsten ..... Cambridge

† Aruguete, Alayne ..... Sandstone
† Aruguete, Jose ..... Sandstone
‡ Berge, Harry L. ..... Mora
‡ Berglund, Alvin E. ..... Cambridge
‡ Brettingen, Larry J. ..... Mora
Buentipo, Benigno ..... Mora
Bunker, Bevan W. ..... Anoka
‡ Burseth, Edgar C. ..... Mora
‡ Deason, Keith B. ..... Chisago City
Doebler, Myron I. ..... Princeton
Erickson, Carlton ..... Lindstrom
Gailitis, Veronika M. ..... St. Paul
Grinvalds, Anna O. ..... Cambridge
‡ Hartzler, Paul L. ..... Cambridge
‡ Hovde, Gordon W. ..... Chisago City
Huber, Robert W. ..... St. Croix Falls, WI
Hubin, Edwin G. ..... Sandstone
† Kelsey, Carleton G. ..... St. Paul
‡ La Kosky, Randall A. ..... Braham
† Lamusga, David J. ..... Minnetonka
‡ Larson, Gerald E. ..... Cambridge
‡ Lindquist, Dale C. ..... Lindstrom
‡ Mach, Ralph F. ..... Pine City
‡ Magnuson, Raymond C. ..... Cambridge
Metcalf, Norman ..... Princeton
‡ Nelson, Luther A. ..... Rush City
‡ Nordman, Willard F. ..... Mora
Nygren, William T. ..... Braham
‡ Overgaard, Peter H. ..... Lindstrom
‡ Peterson, Alvin C. ..... Mora
Pivac (Popovich) Dragojla ..... Milwaukee, WI
‡ Reiners, Gary ..... Cambridge
‡ Ristic, Miodrag ..... Cambridge
†‡ Roehlke, Arthur E. ..... Elk River
‡ Runquist, Richard ..... Cambridge
† Schut, John W. ..... Anoka
‡ Seecamp, Carsten H. ..... Cambridge
Sommer, R. K. ..... Elk River
† Spurzem, Raymond J. ..... Anoka
†‡ Stratte, Alf K. ..... Pine City
‡ Tesch, Gordon H. ..... Elk River
Textor, Jerome ..... Minnetonka Village
‡ Travis, Richard C. ..... Elk River

FREEBORN COUNTY MEDICAL SOCIETY

Freeborn County
Regular meetings, third Thursday of even months
Annual meeting, December
Number of members 36

PRESIDENT
Barr, Lowell W. ..... Albert Lea
SECRETARY
Ellertson, Leonard M. ..... Albert Lea

‡ Barr, Lowell C. ..... Albert Lea
‡ Barr, Lowell W. ..... Albert Lea
‡ Bartness, John E. ..... Albert Lea
‡ Blumer, Arlo R. ..... Albert Lea
Buege, William ..... Albert Lea
† Burns, Catherine ..... Excelsior
*† Calhoun, Frank W. ..... Albert Lea
Campbell, John C. ..... Albert Lea
Cole, George A. ..... Albert Lea
‡ Demo, Robert A. ..... Albert Lea
Donovan, Daniel L. ..... New Brighton
‡ Egge, Sanford G. ..... Albert Lea
‡ Ellertson, Leonard M. ..... Albert Lea
Erdal, Ove A. ..... Albert Lea
Gamble, Elbert J. ..... Roseville
‡ Gill, Theodore M. ..... Albert Lea
‡ Halvorson, Harold C. ..... Albert Lea
‡ Hansen, Theodore M. ..... Albert Lea
‡ Keil, Marcus A. ..... Albert Lea
† Leopard, Brand A. ..... Brownsville, TX
‡ Menefee, Edward C. ..... Albert Lea
Myers, Theodore P. ..... Albert Lea
‡ Neel, Harry B. ..... Albert Lea
‡ Nelson, Clayton E. J. ..... Albert Lea
‡ Nesheim, Martin O. ..... Albert Lea
‡ Palmer, Clinton F. ..... Albert Lea
Rose, Cordt ..... Albert Lea
‡ Schmidt, Ruben F. ..... Alden
‡ Shepard, Richard ..... Albert Lea
‡ Sherman, Alfred G. ..... Albert Lea
*‡ Snyder, C. D. ..... Kiester
‡ Steiner, Leon E. ..... Albert Lea
Stoker, Lynn C. ..... Albert Lea
Thompson, Thoburn F. ..... Albert Lea
‡ Treanor, Thomas A. ..... Albert Lea
‡ Whitson, Sidney A. ..... Albert Lea
‡ Wilcox, G. Charles ..... Albert Lea
‡ Willie, James A. ..... Albert Lea

GOODHUE COUNTY MEDICAL SOCIETY

Goodhue County
Regular meeting, April and November
Annual meeting, November
Number of members 24

PRESIDENT
Douglass, Jesse E. ..... Cannon Falls
SECRETARY
Friedrich, Bradford ..... Red Wing

‡ Akins, Willard M. ..... Red Wing
‡ Billings, Harry H. ..... Red Wing
Biltz, John F. ..... Red Wing
†‡ Brusegard, James F. ..... Red Wing
‡ Cant, Wilbur F. ..... Red Wing
‡ Delahunty, John R. ..... Red Wing
Douglass, Jesse E. ..... Cannon Falls
Falls, John L. ..... Red Wing
Friedrich, Bradford E. ..... Red Wing
‡ Halvorson, James W. ..... Zumbrota
‡ Hartnagel, Grant F. ..... Red Wing
‡ Hawley, George M. B. ..... Red Wing
‡ Jackish, George E. ..... Red Wing
‡ Juers, Edward H. ..... Red Wing
‡ Kuehner, Marvin E. ..... Red Wing
‡ Larson, Oliver E. H. ..... Zumbrota
Marshall, John F. ..... Pine Island
‡ Molenaar, Robert E. ..... Cannon Falls
‡ Rayner, Ralph R. ..... Red Wing
‡ Roth, Charles W. ..... Red Wing
‡ Sander, John L. ..... Red Wing
Schroeder, Glenn E. ..... Red Wing
‡ Sherman, Royal V. ..... Red Wing
Walter, William E. ..... Wanamingo
‡ Wasmund, Clarence W. ..... Red Wing
‡ Williams, Marland R. ..... Cannon Falls

HEADWATERS MEDICAL SOCIETY

Beltrami, Clearwater and Lake of the Woods Counties
Regular meetings to be determined
Annual meeting, 2nd Saturday in September
Number of members 22

PRESIDENT
Lundsten, Leslie C. ..... Bemidji

SECRETARY
Gregoire, Earl ..... Bemidji

Brink, Adlai A. ..... Baudette
Deweese, Joel T. ..... Bemidji
Deweese, Wilford J. ..... Bemidji
Franklin, Gordon W. ..... Northome
Gregoire, Earl ..... Bemidji
Griffin, John W. ..... Bemidji
*† Groschupf, Theophilus P. ..... Bemidji
Hildebrand, John E. ..... Bemidji
Hoganson, Donald E. ..... Bemidji
Janecky, Allen G. ..... Baudette
† Johnson, Einer W. ..... Bemidji
† Larson, Leroy J. ..... Bagley
Lundsten, Leslie C. ..... Bemidji
Martin, Frederick F. ..... Bagley
Palmer, Harry A. ..... Blackduck
Pearson, Harris L. ..... Bagley
Reeber, Erick ..... Bagley
Reid, Howard ..... Bemidji
Roholt, Hartvig B. ..... Bemidji
Stengel, Thomas A. ..... Bemidji
Thompson, James R. ..... Bemidji
Whittemore, Dexter D. ..... Bemidji
Wohfield, Dwayne L. ..... Bemidji

HENNEPIN COUNTY MEDICAL SOCIETY

Hennepin County
Regular meetings, first Monday of the Months of
October, January, March and May, except when
otherwise designated
Annual meeting, first Monday in October
Number of members 1455

PRESIDENT
Blake, Paul S. ..... Minneapolis
SECRETARY
Mankey, James C. ..... Minneapolis
EXECUTIVE SECRETARY
Cook, Thomas P., Mr. ..... Minneapolis
ADMINISTRATIVE ASSISTANT
Hoban, Thomas W., Mr. ..... Minneapolis
Abramson, Burton I. ..... Minneapolis
Abramson, Milton ..... Minneapolis
‡ Abullarade, Jose A. ..... Minneapolis
‡ Abuzzahab, Faruk S. ..... Minneapolis
‡ Adams, Brandon, L. W. ..... Minneapolis
‡ Adams, Richard I. ..... Minneaplois
‡ Adicoff, Arnold ..... Minneapolis
‡ Adkins, C. Douglas ..... Minneapolis
‡ Adkins, James T. ..... Coon Rapids
‡ Agustsson, Hreidar ..... Minneapolis
‡ Ahern, Eugene E. ..... Minneapolis
Akbar, Sajady ..... Minneapolis
‡ Aksoy, Mustafa M. ..... St. Paul
‡ Alari, Heino ..... Excelsior
‡ Alexander, Harlan A. ..... Minneapolis
†‡ Aling, Charles A. ..... Minneapolis
‡ Allen, James R. ..... Minneapolis
Alter, Milton ..... Minneapolis
*† Altnow, Hugo O. ..... Miami, FL
‡ Amatuzio, Donald S. ..... Minneapolis
‡ Amren, Don P. ..... Minneapolis
‡ Anderegg, Alfred F. ..... Minneapolis
Andersen, James G. ..... Minneapolis
‡ Andersen, Robert C. ..... Minneapolis
‡ Anderson, Arnold S. ..... Minneapolis
‡ Anderson, David M. ..... Minneapolis
†‡ Anderson, Ernest R. ..... Minneapolis
‡ Anderson, Frank J. ..... Minneapolis
Anderson, John A. ..... Minneapolis
†‡ Anderson, Karl W. ..... Excelsior
‡ Anderson, Quentin N. ..... Minneapolis
Anderson, Richard W. ..... Minneapolis
Anderson, Roger E. ..... Minneapolis
Anderson, Roger L. ..... Minneapolis
Anderson, Thomas P. ..... Minneapolis
Anderson, U. Schuyler ..... Fort Snelling
Anderson, Wallace E. ..... Minneapolis
‡ Anderson, William H. ..... Minneapolis
Anderson, William T. ..... Minneapolis
Anderson, W. Robert ..... Minneapolis
Andre, James C. ..... Minneapolis
†‡ Andreassen, Einar C. ..... Minneapolis
‡ Andreassen, Rolf L. ..... Minneapolis
‡ Andresen, Karl d'A ..... Minneapolis
‡ Ankner, Frank J. ..... Minneapolis
‡ Anonsen, Richard E. ..... Minneapolis
Anselment, Lois A. ..... Excelsior
† Arends, Archabald L. ..... Minneapolis
Arensen, Jeffrey A. ..... Minneapolis
‡ Arey, Stuart Lane ..... Minneapolis
‡ Arhelger, Stuart W. ..... Minneapolis
‡ Arlander, Clarence E. ..... Minneapolis
Arlander, Thomas R. ..... Minneapolis
‡ Arling, Leonard S. ..... Minneapolis
‡ Arms, James J. ..... Minneapolis
Armstrong, Byron H. ..... Minneapolis
† Arnold, Ann W. ..... Minneapolis
Arnold, Thomas B. ..... Minneapolis
Aughenbaugh, John W. ..... Minneapolis
† Aust, John C. ..... Morgantown, WV
‡ Avant, Robert F. ..... Minneapolis
Azad, Manouchehr ..... Minneapolis
‡ Backus, Reno E. ..... Minneapolis
‡ Baggenstoss, Osmond J. ..... Minneapolis
‡ Bagley, Russell W. ..... Minneapolis
†‡ Baken, Melvin P. ..... St. Paul
Baken, Melvin P., Jr. ..... Minneapolis
Baker, Abe B. ..... Minneapolis
‡ Baker, C. Camak ..... Minneapolis
‡ Baker, Daniel R. ..... Minneapolis
Baker, Lowell ..... Minneapolis
‡ Baker, Milton E. ..... Minneapolis
Bakke, Arnold C. ..... Minneapolis
Balcos, Emmanuel C. ..... Minneapolis
‡ Balkin, Samuel G. ..... Minneapolis
‡ Balkins, John W. ..... Minneapolis
‡ Balogh, Charles J. ..... Minneapolis
Bandt, Calvin M. ..... Minneapolis
† Bank, Harry E. ..... Minneapolis
Banovetz, John D. ..... Minneapolis
‡ Barnett, Robert M. ..... Minneapolis
‡ Barno, Alex ..... Minneapolis
‡ Barr, Maxwell M. ..... Minneapolis
* Barr, Robert N. ..... Minneapolis
‡ Barrett, Patrick J. ..... Minneapolis
‡ Barron, Jesse J. ..... Minneapolis
†‡ Barron, Moses ..... Beverly Hills, CA
‡ Barry, George J. ..... Edina
Bart, Bruce J. ..... Minneapolis
Baumgartner, C. John ..... Minneapolis
‡ Beach, Northrop ..... Minneapolis
Beard, Archibald H., Jr. ..... Minneapolis
Becklund, Roger W. ..... Minneapolis
‡ Beeman, John A. ..... Minneapolis
Beirstein, Samuel ..... Minneapolis
† Beiswanger, Richard H. ..... Edina
‡ Bell, Donald C. ..... Minneapolis
Bellville, Titus P. ..... Minneapolis
‡ Bendel, Richard P. ..... Minneapolis
Bendel, William L., Jr. ..... Coon Rapids
Benesh, Louis A. ..... Minneapolis
‡ Benjamin, Edwin G. ..... Minneapolis
‡ Benjamin, Harold G. ..... Minneapolis
Benjamin, Richard D. ..... Minneapolis
‡ Benjamin, Robert B. ..... Minneapolis
Bensman, Alan S. ..... Minneapolis
‡ Bentz, Herman D. ..... Anoka
‡ Berestka, Stephen J. ..... Minneapolis
Berg, Clinton C. ..... Excelsior
Berger, Alex G. ..... Minneapolis
‡ Bergh, George S. ..... Minneapolis
Bergh, Solveig M. ..... Minneapolis

Hennepin County Medical Society *(Continued)*

‡ Berglund, Eldon B. ..... Minneapolis
‡ Bergquist, James R. ..... Minneapolis
Bergstrom, Ralph W., Jr. ..... Maple Plain
† Bergstrom, William J. ..... Minneapolis
† Berkwitz, Nathaniel J. ..... Minneapolis
Berman, David A. ..... Minneapolis
Berman, Reuben ..... Minneapolis
Bernstein, Dorothy M. ..... Minneapolis
Bernstein, Irving C. ..... Minneapolis
‡ Berris, Harold ..... Minneapolis
Berry, Ronald N. ..... Minneapolis
‡ Berzins, Rainis ..... Minneapolis
†‡ Bessesen, Alfred N. ..... Minneapolis
‡ Bevis, William D. ..... Minneapolis
Bieger, R. Cyril ..... Minneapolis
Biery, M. Barbara ..... Minneapolis
Bieter, Raymond N. ..... Minneapolis
‡ Bilgutay, Aydin M. ..... Minneapolis
Bilka, Paul J. ..... Minneapolis
Billman, Herbert R. ..... Minneapolis
‡ Binder, Manuel R. ..... Minneapolis
Bittick, Wilbur H. ..... Minneapolis
‡ Blackard, Clyde E. ..... Minneapolis
‡ Blake, Allan J. ..... Hopkins
‡ Blake, James A. ..... Hopkins
‡ Blake, Paul S. ..... Minneapolis
Bloch, Henry S. ..... Minneapolis
‡ Bloedel, Traugott J. ..... Osseo
‡ Blomberg, Robert D. ..... Minneapolis
‡ Bloom, David ..... Minneapolis
Bloom, Norman B. ..... Minneapolis
‡ Blumenthal, Malcolm N. ..... Minneapolis
‡ Boardman, Peter J. ..... Wayzata
Bofenkamp, Benjamin ..... Minneapolis
*†‡ Bohn, Donald G. ..... Minneapolis
†‡ Boies, Lawrence R., Sr. ..... Hopkins
Bolt, Donald A. ..... Minneapolis
‡ Bonewell, George W. ..... Minneapolis
‡ Borman, Chauncey N. ..... Minneapolis
† Borowicz, Leonard A. ..... Minneapolis
Bouthilet, Florence J. ..... Minneapolis
† Bowers, Gordon G. ..... Excelsior
‡ Bowlin, Paul F. ..... Minneapolis
† Boynton, Ruth E. ..... Miami, FL
† Boyum, Allan J. ..... Minneapolis
Bradford, David S. ..... Minneapolis
Bradley, Jeanne B. ..... Minneapolis
Bradley, John G. ..... Minneapolis
Bradley, William E. ..... Minneapolis
‡ Brandt, Henry E. ..... Minneapolis
‡ Bransford, Paul W. ..... Minneapolis
‡ Brauer, William W. ..... Minneapolis
‡ Braun, Rene ..... Minneapolis
‡ Breitenbucher, Robert B. ..... Minneapolis
†‡ Brekke, Harvey J. ..... Minneapolis
‡ Brennan, Joseph G. ..... Minneapolis
Brill, Alice K. ..... Minneapolis
‡ Briones, Bienvenido R. ..... Hopkins
‡ Bromer, Michael D. ..... Minneapolis
† Brooks, Charles N. ..... Wayzata
‡ Brown, John H. ..... Minneapolis
‡ Brown, William D., Jr. ..... Minneapolis
Brownfield, James A. ..... Minneapolis
‡ Buchstein, Harold F. ..... Minneapolis
‡ Buckley, Joseph J. ..... Minneapolis
‡ Bugby, Robert D. ..... Minneapolis
‡ Bugenstein, Robert H. ..... Minneapolis
‡ Buie, Louis A., Jr. ..... Minneapolis
‡ Bundt, Robert E. ..... Minneapolis
‡ Buran, David J. ..... Minneapolis
‡ Burchell, Howard G. ..... Minneapolis
Burke-Strickland, Martha ..... Minneapolis
Burkholder, Dayton D. ..... Anoka
‡ Burnham, Wesley H. ..... Minneapolis
Burton, Thomas P. ..... Minneapolis
‡ Cable, Morris L. ..... Minneapolis
† Cabot, Clyde M. ..... Deerfield Beach, FL
‡ Calin, S. Hartley ..... Minneapolis
Cameron, Bruce P. ..... Minneapolis
† Cameron, Isabell L. ..... Minneapolis
‡ Campbell, Denis V. ..... Minneapolis
Campbell, Marilyn R. M. ..... Minneapolis
‡ Campbell, Orwood J. ..... Minneapolis
† Campbell, Ronald G. ..... Minneapolis
‡ Card, William H. ..... Minneapolis
Cardle, James G. ..... Minneapolis
‡ Cardle, John B. ..... Minneapolis
‡ Carlander, Lester W. ..... Minneapolis
‡ Carlson, Charles V. ..... Mound
Carlson, David J. ..... Minneapolis
‡ Carlson, Lawrence ..... Minneapolis
‡ Carr, William J. ..... Minneapolis
‡ Carrier, Thomas C. ..... Minneapolis
‡ Caspers, Carl G. ..... Minneapolis
‡ Cauble, Charles F. ..... Minneapolis
†‡ Cavanor, Frank T. ..... Minneapolis
‡ Cavert, H. Mead ..... Minneapolis
‡ Ceder, Elmer T. ..... Minneapolis
‡ Cella, Joseph A. ..... Minneapolis
‡ Chadbourn, Wayne A. ..... Minneapolis
Challman, S. Alan ..... Minneapolis
‡ Chandler, William M. ..... Minneapolis
‡ Chedister, Charles R. ..... Minneapolis
Chervenak, William A. ..... Marine-on-St. Croix
‡ Chesler, Merrill D. ..... Minneapolis
Child, Sherman B. ..... Minneapolis
† Chilgren, Keith V. ..... Minneapolis
‡ Chisholm, Tague C. ..... Minneapolis
Chou, Shelley N. ..... Minneapolis
Christensen, Llewellyn E. ..... Minneapolis
Christenson, Leland R. ..... Maple Plain
Christgau, Roger A. ..... Minneapolis
Christian, William L. ..... Minneapolis
‡ Clark, Malcolm D. ..... Minneapolis
Clark, Robert S. ..... Minneapolis
Clay, Lyman B. ..... Minneapolis
‡ Cline, David W. ..... Minneapolis
‡ Cochrane, Ray F. ..... Minneapolis
Coe, John I. ..... Minneapolis
‡ Cohan, Richard C. ..... Minneapolis
‡ Cohen, Bernard A. ..... Minneapolis
Cohen, Ephraim B. ..... Minneapolis
‡ Cohen, Henry W. ..... Wayzata
‡ Cohen, Summer S. ..... Minneapolis
‡ Cole, James S. ..... Minneapolis
Coleman, Thomas P. ..... Ethiopia
‡ Conlin, F. Dixon ..... Minneapolis
‡ Conlon, Daniel C. ..... Minneapolis
† Connor, David G. ..... Minneapolis
‡ Cooper, John P. ..... Minneapolis
‡ Cooper, Robert R. ..... Minneapolis
† Corniea, Albert D. ..... Minneapolis
Correa, Dale H. ..... Minneapolis
Corson, Wilfred A. ..... Minneapolis
‡ Cortez, Daniel P. ..... Minneapolis
‡ Coulter, Harold E. ..... Minneapolis
Cowan, Donald W. ..... Minneapolis
Craig, M. Elizabeth ..... Minneapolis

Continued on Next Page

Hennepin County Medical Society *(Continued)*

†‡ Cranmer, Richard R. ..... Laguna Hills, CA
Cranston, Robert W. ..... Minneapolis
‡ Creevy, Charles D. ..... Minneapolis
† Crossley, Kent B. ..... Minneapolis
‡ Crowley, Leonard V. ..... Minneapolis
‡ Cullado, Andrionico F. ..... Minneapolis
Culligan, Leo C. ..... Minneapolis
‡ Cundy, Donald T. ..... Minneapolis
‡ Curran, John P. ..... Anoka
Cushing, Richard T. ..... Minneapolis
† Cutts, George ..... Minneapolis
‡ Daggett, Donald R. ..... Minneapolis
Dahl, James C. ..... Minneapolis
† Dahl, John A. ..... Minneapolis
Dahlstrom, Donald D. ..... Minneapolis
† Daniel, Donald H. ..... Minneapolis
Daniels, Clarke G. ..... Minneapolis
‡ Danyluk, Michael ..... Minneapolis
Dargay, Cyril P. ..... Minneapolis
‡ Daumann, Roy E. ..... Minneapolis
‡ David, Reuben ..... Hopkins
‡ Davis, Michael W. ..... Minneapolis
Davis, Thomas H. ..... Minneapolis
Dawson W. John, Jr. ..... Minneapolis
†‡ Dedeker, Kenneth L. ..... Minneapolis
Delzell, Allen W. ..... Minneapolis
‡ Diamond, Robert A. ..... Minneapolis
Dickman, Roy W. ..... Minneapolis
Diefenbach, Eugene J. ..... Minneapolis
‡ Diego, Benito B. ..... Fridley
† Diehl, Harold S. ..... New York, NY
Diehl, James J. ..... Minneapolis
‡ Dierker, Heinrich A. ..... Minneapolis
† Diessner, Henry D. ..... Hopkins
Dimants, Janis, Jr. ..... Minneapolis
‡ Doan, Robert E. ..... Wayzata
† Dobrin, Dale T. ..... Minneapolis
Docherty, John A. ..... Minneapolis
‡ Donatelle, Edward P. ..... Minneapolis
† Dorge, Richard ..... Minneapolis
Dornbach, Robert A. ..... Minneapolis
‡ Dorsey, George C., Jr. ..... Minneapolis
‡ Dorsey, William E. ..... Minneapolis
Doscherholmen, Alfred ..... Minneapolis
‡ Dougan, Jerome W. ..... Minneapolis
DoVale, Joao M. ..... Edina
† Doxey, Gilbert L. ..... Minneapolis
†‡ Dredge, Thomas E., Sr. ..... Minneapolis
†‡ Dredge, Thomas E., Jr. ..... Minneapolis
‡ Drill, Frederick E. ..... Minneapolis
‡ Drill, Herman E. ..... Hopkins
Duffy, John C. ..... Tucson, AZ
Dummer, Donald J. ..... New Brighton
Dumonceau, Roland G. ..... Minneapolis
Duncan, Donald A. ..... Minneapolis
‡ Dunlap, David J. ..... Minneapolis
‡ Dunlap, Earl H. ..... Minneapolis
‡ Dupont, Joseph A. ..... Excelsior
Duryea, Willis M. ..... Minneapolis
‡ Duryea, Willis M., Jr. ..... Minneapolis
‡ Dvorak, Benjamin A. ..... Minneapolis
‡ Dwan, Paul F. ..... Minneapolis
† Dworsky, Samuel D. ..... Minneapolis
Earl, Stephan H. ..... Minneapolis
Ebert, Richard V. ..... Minneapolis
Eckerly, Jean R. ..... Minneapolis
‡ Eder, Walter P. ..... Minneapolis
‡ Edmondson, Hugh A., Jr. ..... Minneapolis
‡ Efteland, Myles E. ..... Minneapolis
† Ehrenberg, Claude J. ..... Boca Raton, FL
‡ Ehrlich, S. Paul ..... Minneapolis
Eich, Matthew A. ..... Minneapolis
Eichenlaub, John E. ..... Minneapolis
‡ Eichhorn, Edmund P., Jr. ..... Minneapolis
Eisenberg, M. Michael ..... Minneapolis
*† Eisenstadt, David H. ..... Minneapolis
‡ Eisenstadt, William S. ..... Minneapolis
Eitel, George D. ..... Minneapolis
Ellingson, Richard B. ..... Minneapolis
Ellington, Anna L. ..... Minneapolis
Ellis, Cassius M. C. ..... Minneapolis
‡ Ellis, John C., Jr. ..... Minneapolis
‡ Ellison, Evan S. ..... Minneapolis
Elwood, Paul M., Jr. ..... Minneapolis
† Emond, Joseph S. ..... Farmington
Emond, Joseph S., Jr. ..... Farmington
‡ Engel, Joseph P. ..... Minneapolis
Engel, William L. ..... Minneapolis
‡ Englund, Elvin F. ..... Minneapolis
† Engstrand, Oscar J. ..... Minneapolis
‡ Engstrom, E. Duane ..... Minneapolis
‡ Engwall, Richard L. ..... Minnetonka
‡ Erickson, Clifford O. ..... Minneapolis
‡ Erickson, Laurence F. ..... Minneapolis
‡ Erickson, Myron E. ..... Minneapolis
†‡ Erickson, Reuben F. ..... Minneapolis
† Ersek, Robert A. ..... Minneapolis
‡ Eselius, Erik P. ..... Minneapolis
‡ Esensten, Sidney ..... Minneapolis
‡ Ettinger, Milton G. ..... Minneapolis
‡ Etzwiler, Donnell D. ..... Minneapolis
†‡ Evans, Edward T. ..... Minneapolis
‡ Everhart, Clarence E., Jr. ..... Minneapolis
Everly, Stephen S. ..... Minneapolis
† Fallon, Virgil T. ..... Minneapolis
Farber Abigail F. ..... Minneapolis
Farber, Roger E. ..... Minneapolis
‡ Farber, Lawrence A. ..... Minneapolis
Farley, Harrison H. ..... Minneapolis
Farrell, T. Edwin ..... Minneapolis
*† Feeney, John M. ..... Excelsior
‡ Feigal, David W. ..... Wayzata
Feinberg, Philip ..... Minneapolis
Feinberg, Samuel B. ..... Minneapolis
‡ Fernandez, Rafael F., Jr. ..... Minneapolis
Fetzek, Albert D. ..... Minneapolis
‡ Field, Charles W. ..... Minneapolis
Fifer, Ellen Z. ..... St. Paul
Fifer, William R. ..... Minneapolis
Filiatrault, L. J. ..... Coon Rapids
Filipovich, Orest N. ..... Minneapolis
‡ Fingerman, David L. ..... Minneapolis
†‡ Fink, Leo W. ..... Minneapolis
‡ Fink, Robert J. ..... Minneapolis
‡ Finkelstein, Joel ..... Minneapolis
Finlayson, Richard E. ..... Minneapolis
†‡ Fischer, Albert P. ..... Minneapolis
† Fisher, Albert P., Jr. ..... Minneapolis
Fisher, Don H. ..... Minneapolis
Fisher, Isadore ..... Minneapolis
Fleming, Dean S. ..... Minneapolis
‡ Fliehr, Richard R. ..... Minneapolis
‡ Flora, George C. ..... Minneapolis
† Florence, David W. ..... Minneapolis
Flory, W. Daniel ..... Minneapolis
Fluegel, John O. ..... Minneapolis
Foker, Leslie W. ..... Minneapolis
Foley, Robert R. ..... Minneapolis
‡ Foley, William A. ..... Minneapolis

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‡ Folsom, Louis B. ..... Minneapolis
Forbes, Edward F. ..... Minneapolis
Ford, W. Harold ..... Hopkins
Fortuny, Ignacio E. ..... Minneapolis
‡ Foster, Orley W. ..... Minneapolis
‡ Fox, James Rogers ..... Edina
‡ Fraley, Elwin E. ..... Minneapolis
‡ Frane, Donald B. ..... Minneapolis
‡ Frane, Gerald T. ..... Minneapolis
‡ Fredlund, Jon S. ..... Anoka
‡ Freeman, Craig W. ..... Minneapolis
Freeman, Donald W. ..... Minneapolis
French, Lyle A. ..... Minneapolis
‡ Frey, Richard J. ..... Minneapolis
Friberg, Joseph B. ..... Minneapolis
Fried, Louis A. ..... Minneapolis
† Friedell, Aaron ..... Minneapolis
Friedell, George ..... Minneapolis
‡ Friedman, Harry S. ..... Minneapolis
‡ Friend, Charles A. ..... Minneapolis
‡ Frost, John B. ..... Minneapolis
‡ Fruchtman, Stanley A. ..... Minneapolis
‡ Frys, Russell N. ..... Minneapolis
Fuglestad, Edson V. ..... Minneapolis
‡ Fuglestad, J. Roald ..... Minneapolis
† Fuller, Alice H. ..... Minneapolis
†‡ Funk, Victor K. ..... Hopkins
Furman, L. Christine ..... Minneapolis
Gaard, Richard C. ..... Robbinsdale
‡ Galbraith, Richard F. ..... Minneapolis
Galejs, Aina ..... St. Paul
Gallagher, Larry J. ..... Mound
‡ Gallett, Lester E. ..... Minneapolis
† Galligan, Margaret Mary D. ..... Minneapolis
Galway, Charles F. ..... Minneapolis
Gamble, William G. ..... Minneapolis
‡ Gannon, Paul G. ..... Minneapolis
‡ Garamella, Joseph J. ..... Minneapolis
Garetz, Floyd K. ..... Minneapolis
‡ Garske, George L. ..... Minneapolis
Garten, Joseph L. ..... Minneapolis
‡ Garvey, James T. ..... Minneapolis
Gasik, Joseph M. ..... Minneapolis
‡ Gaviser, David ..... Minneapolis
Geis, LeRoy F. ..... Minneapolis
Geller, Joseph ..... Minneapolis
George, Vane P., Jr. ..... Le Sueur
Gerster, Paul W. ..... Anoka
Gesundheit, Sim ..... Minneapolis
Gibbs, Robert W. ..... Minneapolis
‡ Giebenhain, John N. ..... Minneapolis
‡ Giere, Joseph C. ..... Minneapolis
† Giere, Richard W. ..... Minneapolis
Gilbert, Maurice G. ..... Minneapolis
Gilbertsen, A. Sigrid ..... Minneapolis
Gilbertsen, Victor A. ..... Minneapolis
Gilles, Paul J. ..... Minneapolis
† Gingold, Benjamin A. ..... Minneapolis
Glaeser, John H. ..... Minneapolis
‡ Godfrey, H. Wilson ..... Minneapolis
‡ Goehl, Reinhold O., Jr. ..... Minneapolis
Goetz, Frederick C. ..... Minneapolis
Gokcen, Barbara W. ..... Minneapolis
Gokcen, Muharrem ..... Minneapolis
† Goldberg, Isadore M. ..... Minneapolis
Goldberg, Marvin E. ..... Minneapolis
‡ Goldberg, Stanley M. ..... Minneapolis
Goldfarb, Benjie L. ..... Minneapolis
‡ Goldfarb, Mace G. ..... Minneapolis
†‡ Goldman, Theodore I. ..... Minneapolis
‡ Goldner, Meyer Z. ..... Minneapolis
Goldstein, Alan L. ..... Hopkins
‡ Good, Gary ..... Minneapolis
‡ Goodale, Robert L., Jr. ..... Minneapolis
‡ Goodchild, William R. ..... Minneapolis
Gordon, John R. ..... Minneapolis
‡ Gordon, Sewell S. ..... Minneapolis
Gozum, Ekrem ..... Minneapolis
Grados, Carlos ..... Coon Rapids
Grage, Theodor ..... Minneapolis
Graham, John J. ..... Minneapolis
‡ Granquist, Richard D. ..... Minneapolis
‡ Grant, James B. ..... Minneapolis
Grant, Suzanne ..... Minneapolis
† Gratzek, Frank R. ..... Anoka
† Gray, Royal C. ..... Minneapolis
Greden, John F. ..... Silver Springs, MD
Green, Clayton R. ..... Excelsior
Green, Robert A. ..... Minneapolis
Greenberg, Albert J. ..... Minneapolis
‡ Greene, Leonard H. ..... Minneapolis
‡ Greenfield, Irving ..... Minneapolis
Greenwald, Stephen M. ..... Minneapolis
¶ Greisheimer, Esther M. ..... Philadelphia, PA
† Grimes, Marian ..... Minneapolis
‡ Grimmell, Francis J. ..... Minneapolis
† Grismer, Jerome T. ..... Wauwatosa, WI
Grossling-Freudenberg, Sergio ..... Minneapolis
Grube, David W. ..... Minneapolis
‡ Gruys, Robert I. ..... Edina
Guerrero, Rafael A. ..... Minneapolis
Gullickson, Glenn, Jr. ..... Minneapolis
‡ Gunlaugson, Frederick G. ..... Minneapolis
‡ Gustafson, Paul O. ..... Minneapolis
Gustafson, Robert W. ..... Mound
‡ Gustason, Harold T. ..... Minneapolis
Gustilo, Ramon B. ..... Minneapolis
Haas, John W. ..... Minneapolis
Haberer, Helen R. ..... Stacy
‡ Haberle, Charles A. ..... Minneapolis
‡ Hagen, Kristofer ..... Minneapolis
‡ Hagen, Wayne S. ..... Minneapolis
‡ Haglin, John J. ..... Minneapolis
‡ Hakim, Ali A. ..... Minneapolis
‡ Hall, Arthur M. ..... Minneapolis
‡ Hall, Harry B. ..... Minneapolis
‡ Hall, Loren J. ..... Minneapolis
‡ Hall, Wendell H. ..... Minneapolis
Hallin, Roger P. ..... Worthington
Hambidge, Gove, Jr. ..... Minneapolis
‡ Hamel, Arnold L. ..... Minneapolis
‡ Hamel, Joseph I. ..... Minneapolis
Hammerstrom, Robert N. ..... Minneapolis
‡ Handler, Seymour ..... Minneapolis
Hanisch, Edward C., Jr. ..... Minneapolis
‡ Hansen, Cyrus O. ..... Minneapolis
†‡ Hansen, Erling W. ..... Minnetonka
† Hansen, Olga S. ..... Minneapolis
‡ Hansen, Rollin M. ..... Mineapolis
‡ Hanske, Edward A. ..... Minneapolis
‡ Hanson, Harlow J. ..... Minneapolis
Hanson, Harold B. ..... St. Paul
‡ Hanson, Harold W. ..... Minneapolis
† Hanson, Henry V. ..... Green Valley, AZ
†‡ Hanson, Malcolm B. ..... Osseo
‡ Hanson, Mark C. L. ..... Minneapolis
Hanson, Mildred S. ..... Minneapolis
‡ Hanson, Stephen L. ..... Minneapolis

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Hennepin County Medical Society *(Continued)*

† Hanson, William A. H. ..... Minnetonka
Hanson, William B. ..... Minneapolis
† Harrington, Donald P. ..... Minneapolis
Harris, Leon D. ..... Bloomington
Harrison, William C. ..... Minneapolis
‡ Hartig, Paul R. ..... Minneapolis
Hartman, Evelyn E. ..... Minneapolis
‡ Hartwig, John A. ..... Minneapolis
Harty, Jerome L. ..... Fridley
Harvey, Clyde B. ..... Minneapolis
‡ Hass, Frederick M. ..... Minneapolis
‡ Hastings, Donald W. ..... Minneapolis
‡ Hauge, Erling T. ..... Minneapolis
‡ Haugen, George W. ..... Minneapolis
Haugen, John A. ..... Minneapolis
‡ Hauser, Donald C. ..... Minneapolis
‡ Havel, Robert J. ..... Minneapolis
‡ Haven, Walter K. ..... Minneapolis
† Hawkinson, Raymond P. ..... Minneapolis
‡ Hay, Lyle J. ..... Minneapolis
‡ Hays, Albert T. ..... Minneapolis
‡ Haywa, E. William ..... Minneapolis
†‡ Head, Douglas P. ..... Minneapolis
‡ Hebbel, Robert ..... Minneapolis
‡ Hedrick, William L. ..... Minneapolis
‡ Heinz, John N. ..... Minneapolis
Helgaas, Steffen A. ..... Farmington
Hempel, Dean J. ..... Minneapolis
‡ Henrikson, Earl C. ..... Minneapolis
† Herbert, Willis L. ..... Minneapolis
‡ Hess, Carroll N. ..... Minneapolis
‡ Heupel, Hermann W. ..... Minneapolis
‡ Hewitt, Marshall I. ..... Minneapolis
Hiatt, John A. ..... Minneapolis
‡ Hickok, David F. ..... Minneapolis
Hildebrandt, Walter C. ..... Minneapolis
‡ Hilgedick, William R. ..... Minneapolis
Hilgermann, George ..... Minneapolis
‡ Hill, David L. ..... Minneapolis
‡ Hill, Earl ..... Minneapolis
‡ Hill, Elmer M. ..... Minneapolis
‡ Hiller, Bruce H. ..... Minneapolis
‡ Hitchcock, Claude R. ..... Minneapolis
‡ Hodges, Kenneth V. ..... Minneapolis
‡ Hoffert, Henry E. ..... Minneapolis
‡ Hoffman, Neil R. ..... Minneapolis
† Hoffman, Roy A. ..... Minneapolis
‡ Hoffman, Walter Lees ..... Minneapolis
‡ Hofmann, Gerald N. ..... Minneapolis
‡ Holm, Donald F. ..... Minneapolis
‡ Holmberg, Conrad J. ..... Minneapolis
Holten, David R. ..... Minneapolis
Holzapfel, Fred C. ..... Minneapolis
‡ Hopperstad, J. Jerome ..... Minneapolis
‡ Hoppes, Emerson E. ..... Minneapolis
‡ Horecki, Henry ..... Minneapolis
Horns, Howard L. ..... Minneapolis
‡ Horns, Norman ..... Minneapolis
‡ Horns, Richard C. ..... Minneapolis
Horowitz, Arthur J. ..... Minneapolis
Hoseth, Wayne L. ..... Minneapolis
House, James H. ..... Minneapolis
Householder, James R. ..... Minneapolis
Hovland, Melvin L. ..... Minneapolis
‡ Hovland, Richard D. ..... Minneapolis
† Howard, Richard J. ..... Edina
Howard, Solomon E. ..... Minneapolis
‡ Howell, Carter W. ..... Minneapolis
‡ Howell, John L. ..... Minneapolis
‡ Hoyt, C. Sherman ..... Minneapolis
*† Huenekens, Edgar J. ..... Minneapolis
‡ Huff, John S. ..... Minneapolis
‡ Hulteng, Donald B. ..... Fridley
‡ Hurr, Maland C. ..... Minneapolis
‡ Hustad, Edward G. ..... Minneapolis
‡ Hymes, Alan C. ..... Minneapolis
†‡ Hymes, Charles ..... Minneapolis
Ide, Arthur W., Jr. ..... Minneapolis
‡ Idstrom, Linneus G. ..... Minneapolis
‡ Indeck, Walter ..... Minneapolis
Ingalls, Edgar G. ..... Minneapolis
‡ Iverslie, Philip C. ..... Minneapolis
Iverson, Eleanor B. ..... Minneapolis
‡ Iverson, Rolf M. ..... Minneapolis
‡ Jackson, J. Albert ..... Minneapolis
Jackson, Richard L. ..... Minneapolis
‡ Jacobson, Leslie W. ..... Minneapolis
‡ Jacobson, Loren J. ..... Minneapolis
Jacobson, Wyman E. ..... St. Louis Park
‡ Jaffe, Manuel O. ..... Minneapolis
‡ Janda, George W., Jr. ..... Minneapolis
Jay, Alan R. ..... Temple, TX
‡ Jefferies, William L. ..... Minneapolis
‡ Jensen, Nathan K. ..... Minneapolis
‡ Jensen, Paul A. ..... Minneapolis
Jensen, Reynold A. ..... Minnetonka
Jepson, William W. ..... Minneapolis
Jerome, Bourne ..... Minneapolis
Jerome, Elizabeth B. K. ..... Minneapolis
‡ Jeub, Robert P. ..... Minneapolis
Jinkins, Roger E. ..... Excelsior
Johnson, Aldridge F. ..... St. Paul
Johnson, Angelo G. ..... Minneapolis
‡ Johnson, Arthur B. ..... Minneapolis
Johnson, Bradley D. ..... Minneapolis
Johnson, David R. ..... Minneapolis
‡ Johnson, Donald A. ..... Minneapolis
‡ Johnson, Edward A. ..... Minneapolis
‡ Johnson, Frank E. ..... Minneapolis
‡ Johnson, Gordon E. ..... Minneapolis
‡ Johnson, Harry A., Jr. ..... Minneapolis
†‡ Johnson, James A. ..... Minneapolis
‡ Johnson, John W. ..... Minneapolis
Johnson, Norman P. ..... Minneapolis
Johnson, Norman Paul ..... St. Paul
‡ Johnson, Norton T. ..... Minneapolis
‡ Johnson, Paul E. ..... Wayzata
‡ Johnson, Reinald G. ..... Minneapolis
*† Johnson, Reuben A. ..... Minneapolis
‡ Johnson, Richard S. ..... Minneapolis
‡ Johnson, Richard V. ..... Minneapolis
‡ Johnson, Robert E. ..... Minneapolis
‡ Johnson, Thomas H., Jr. ..... Minneapolis
Johnson, Youbert T. ..... Minneapolis
‡ Johnston, Donald K. ..... Minneapolis
Jones, David G. ..... Minneapolis
†‡ Jones, Herbert W., Jr. ..... Minneapolis
‡ Jones, Richard H. ..... Minneapolis
Jordan, Donald V. ..... Minneapolis
‡ Jorgensen, Harlan ..... Minneapolis
Judd, Allen S. ..... Minneapolis
‡ Judd, Walter H. ..... Washington, DC
Jurdy, Mitchell J. ..... Minneapolis
Kadesky, Harold B. ..... Minneapolis
Kaiser, Harold B. ..... Minneapolis
Kalb, Thomas J. ..... Minneapolis
‡ Kallestad, Leonard L. ..... Minneapolis
Kane, Dennis J. ..... Minneapolis
Kane, Morton C. ..... Minneapolis

Hennepin County Medical Society *(Continued)*

‡ Kane, William J. ..... Minneapolis
‡ Kaplan, Arnold P. ..... Minneapolis
‡ Kaplan, J. Jacob ..... Minneapolis
Kaplan, Martin B. ..... Minneapolis
‡ Karleen, Conrad I. ..... Minneapolis
‡ Karlen, Markle ..... Minneapolis
‡ Kasper, Robert E. ..... Minneapolis
‡ Katkov, Harold ..... Minneapolis
Katz, Beni ..... Minneapolis
Katz, Harry I. ..... Minneapolis
Kaye, Dale R. ..... Minneapolis
Kegel, James F. ..... Minneapolis
†‡ Kelby, Gjert M. ..... Minneapolis
‡ Kelly, John C. ..... Minneapolis
‡ Kelly, John P. ..... Minneapolis
‡ Kelly, John T. ..... Minneapolis
Kelly, William D. ..... Minneapolis
Kennedy, Bryl J. ..... Minneapolis
† Kennedy, Claude C. ..... Minneapolis
‡ Khorsand, Darius ..... Minneapolis
‡ Kieffer, Stephen A. ..... Minneapolis
Kim, Mark K. ..... Minneapolis
Kimmel, George C. ..... Minneapolis
Kind, Allan C. ..... Minneapolis
† King, Frances W. ..... Minnetonka
‡ Kinney, William N. ..... St. Paul
‡ Kiser, Joseph C. ..... Minneapolis
‡ Kjellsen, Douglas L. ..... Minneapolis
‡ Kleven, Lowell H. ..... Minneapolis
‡ Knapp, Miland E. ..... Minneapolis
†‡ Knight, Ralph T. ..... Minneapolis
† Knight, Ray R. ..... Minneapolis
‡ Knobloch, William H. ..... Minneapolis
Knowles, Richard A. ..... Coon Rapids
Knudsen, Helen L. ..... Minneapolis
Kohlhase, Robert E. ..... Minneapolis
‡ Kolars, Charles P. ..... Minneapolis
† Koller, Hermann M. ..... Minneapolis
† Koller, Louis R. ..... Minneapolis
Koller, Robert L. ..... Minneapolis
Kollmorgen, Rodger C. ..... West Point, NY
Koontz, Peter S. ..... Minneapolis
Koos, Gerald W. ..... Minneapolis
Korchik, John P. ..... Minneapolis
Koropchak, Nicholai ..... Minneapolis
‡ Kostich, Nikola D. ..... Minneapolis
Kottke, Frederic J. ..... Minneapolis
† Koucky, Rudolph W. ..... Sagle, ID
‡ Kovack, Freeman D. ..... Minneapolis
‡ Kozak, Michael J. ..... Minneapolis
‡ Krafft, Walter E. ..... Minneapolis
‡ Kragh, Lyle V. ..... Minneapolis
Kramer, Daniel W. ..... Minneapolis
‡ Kremen, Arnold J. ..... Minneapolis
Krieser, Albert E. ..... Minneapolis
Krystosek, Lee A. ..... Minneapolis
†‡ Kucera, Frank J. ..... Hopkins
† Kucera, William J. ..... Santa Barbara, CA
‡ Kump, Warren L. ..... Minneapolis
Kusz, Clarence V. ..... Minneapolis
‡ Kyllo, John E. ..... Minneapolis
Kyllonen, Ronald R. ..... Minneapolis
L'Heureux, Philippe R. ..... Minneapolis
LaBree, John W. ..... Minneapolis
‡ Lagaard, Sheldon M. ..... Minneapolis
† Lajoie, John M. ..... Minneapolis
‡ Lamb, H. Douglas ..... Minneapolis
Lane, Jerald P. ..... Minneapolis
Lang, Leonard A. ..... Minneapolis
Langer, Leonard O., Jr. ..... Minneapolis
‡ Lannon, James B. ..... Minneapolis
†‡ Lapierre, Arthur P. ..... Minneapolis
‡ Larsen, Frank W. ..... Minneapolis
‡ Larson, Allen K. ..... Minneapolis
Larson, Arthur K. ..... Minneapolis
Larson, Carol Ann ..... Minneapolis
‡ Larson, Donald M. ..... Minneapolis
‡ Larson, Ernest J., Jr. ..... Minneapolis
Larson, F. Wilmer ..... Minneapolis
‡ Larson, Lawrence M. ..... Minneapolis
Larson, Loren J. ..... Minneapolis
‡ Larson, Paul N. ..... Minneapolis
‡ Larson, Richard E. ..... Minneapolis
‡ Larson, Roger C. ..... Minneapolis
Larson, Wyllis G. ..... Minneapolis
Latts, Elliot M. ..... Minneapolis
Lauritzen, Herbert ..... Minneapolis
† LaVake, Rae T. ..... Minneapolis
Lawrence, Van S. ..... Minneapolis
Lawrow, John W. ..... Minneapolis
Lawson, Warren R. ..... Minneapolis
‡ Lawton, James J., Jr. ..... Minneapolis
Leavenworth, Richard O., Jr. ..... Minneapolis
Lee, Ju Hao ..... Minneapolis
‡ Leemhuis, Andrew J. ..... Minneapolis
‡ Lees, David C. ..... Minneapolis
‡ Leiferman, Robert J. ..... Minneapolis
Leighton, John S. ..... Minneapolis
Leinonen, Wendla E. ..... Anoka
‡ Lenz, Bernard W. ..... Minneapolis
‡ Lenz, Oa ..... Minneapolis
‡ Leonard, Samuel ..... Minneapolis
Lerner, A. Ross ..... Minneapolis
‡ Leslie, Loren R. ..... Minneapolis
‡ Leslie, W. Robert ..... Minneapolis
Lester, Theodore H. ..... Minneapolis
‡ Letson, Robert D. ..... Minneapolis
‡ Levine, Howard M. ..... Minneapolis
† Levitan, Alexander A. ..... Minneapolis
‡ Levitt, Seymour H. ..... Minneapolis
Lewis, F. Bruce ..... Minneapolis
Lewis, Glenn M., Jr. ..... Minneapolis
‡ Lick, Louis C. ..... Minneapolis
Liebhaber, Henia F. ..... Anoka
‡ Lillehei, James P. ..... Minneapolis
Lillehei, Richard C. ..... Minneapolis
‡ Limbeck, Donald A. ..... Minneapolis
Lindall, Arnold W., Jr. ..... Marine-on-St. Croix
‡ Lindberg, Vernon L. ..... Minneapolis
‡ Lindberg, Winston R. ..... Minneapolis
‡ Lindeland, Arthur T. ..... Minneapolis
‡ Lindemann, Charles E. ..... Minneapolis
‡ Linderholm, Bruce E. ..... Minneapolis
‡ Lindgren, Russell C. ..... Minneapolis
Lindseth, Esten O. ..... Excelsior
‡ Linner, John H. ..... Minneapolis
‡ Linner, Paul W. ..... Minneapolis
Lipschultz, Oscar ..... St. Louis Park
Litman, Abraham B. ..... Minneapolis
‡ Litman, Thomas ..... Minneapolis
Lober, Paul H. ..... Minneapolis
‡ Locke, Murray S. ..... Minneapolis
Lofsness, Stanley V. ..... Minneapolis
Loken, Merle K. ..... Minneapolis
‡ Long, Donlin M. ..... Minneapolis
‡ Lott, Frederick H. ..... Minneapolis
† Lovett, Beatrice R. ..... Minnetonka
Lowe, Douglas A. ..... Minneapolis

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Lowry, Elizabeth C. ..... Minneapolis
Lowry, Jeanette K. ..... Minneapolis
Lowry, Paul T. ..... Minneapolis
‡ Luckey, William T. ..... Minneapolis
‡ Lueck, Wallace W. ..... Minneapolis
†‡ Lufkin, Nathaniel H. ..... Minneapolis
Lukinac, Charles J. ..... Minneapolis
Lund, George W. ..... Minneapolis
Lund, Nancy R. ..... Minneapolis
‡ Lund, Richard R. ..... Minneapolis
*† Lundberg, Ruth I. ..... St. Paul
‡ Lundblad, Rodger R. ..... Minneapolis
† Lundblad, Roy A. ..... Minneapolis
Lundblad, Stanley W. ..... Minneapolis
† Lundeberg, Karl R. ..... Minneapolis
Lundquist, Charles B. ..... Minneapolis
‡ Lundquist, Virgil J. P. ..... Minneapolis
‡ Lynch, Michael F. ..... Minneapolis
Lyon, Fred A. ..... Minneapolis
‡ Lyon, John D. ..... Hopkins
*†‡ Lysne, Henry ..... Minneapolis
Lysne, Richard B. ..... Minneapolis
‡ Lysyj, Anatol ..... Minneapolis
Lyzenga, Anton G. ..... Minneapolis
McCaffrey, F. John ..... Minneapolis
‡ McCampbell, Malcolm D. ..... Minneapolis
‡ McCannel, Malcolm A. ..... Minneapolis
†‡ McCarthy, Donald ..... Minneapolis
McCollister, Robert J. ..... Minneapolis
† McCormick, Donald P. ..... Minneapolis
† McDaniel, Orianna ..... Minneapolis
McFarland, Arthur H. ..... Minneapolis
† McGandy, Robert F. ..... Minneapolis
†‡ McInerny, Maurice W. ..... Minneapolis
† McKelvey, John L. ..... St. Paul
McKelvey, John M. ..... Minneapolis
McKenna, James L. ..... Minneapolis
‡ McKenzie, Charles H. ..... Minneapolis
McKinlay, Gordon L. ..... Minneapolis
‡ McKinley, C. Richard ..... Minneapolis
† McKinney, Frank S. ..... Minneapolis
McLaughlin, Byron H. ..... Minneapolis
McMahon, John E. ..... Minneapolis
McNeil, John J. ..... Minneapolis
‡ McParland, Felix A., Jr. ..... Minneapolis
†‡ McPheeters, Herman O. ..... Minneapolis
McQuoid, David W. ..... Minneapolis
† MacDonald, Daniel A. ..... Minneapolis
MacGibbon, James D. ..... Minneapolis
‡ MacKinnon, Donald C. ..... Minneapolis
†‡ Mach, Frank B. ..... Minneapolis
‡ Mach, John R. ..... Minneapolis
Macheledt, Neil L. ..... Anoka
‡ Madsen, Donald O. ..... Minneapolis
‡ Maeder, Edward C. ..... Minneapolis
‡ Maeder, Edward C., Jr. ..... Minneapolis
‡ Magee, Timothy M. ..... Minneapolis
‡ Malmquist, Carl P. ..... Minneapolis
Mandel, Sheldon L. ..... Minneapolis
Manick, Kenneth P. ..... Minneapolis
‡ Mankey, James C. ..... Minneapolis
Mann, George A. ..... Minneapolis
‡ Manoles, Ellias N. ..... Minneapolis
Manolis, Deane C. ..... Minneapolis
‡ Mark, Aaron L. ..... Minneapolis
‡ Mark, Merle S. ..... Minneapolis
‡ Mark, Peter M. ..... Minneapolis
‡ Marking, George H. ..... Minneapolis
‡ Markland, Colin ..... Minneapolis
Markovitz, Jack M. ..... Minneapolis
‡ Marte, Egon ..... Minneapolis
‡ Martin, Frank E. ..... Minneapolis
‡ Martin, George R. ..... Minneapolis
Martinson, Carl J. ..... Wayzata
Martinson, Elmer J. ..... Wayzata
‡ Maslansky, Robert A. ..... Minneapolis
‡ Massee, Joseph S. ..... Minneapolis
‡ Mastbaum, Leonard I. ..... Minneapolis
Matthews, John A. G. ..... Minneapolis
Maunder, John B. ..... Minneapolis
† Maxeiner, Stanley R. ..... Minneapolis
‡ Maxeiner, S. R., Jr. ..... Minneapolis
Mayberg, Donald M. ..... Minneapolis
Meany, Thomas J. ..... Minneapolis
Mecklenburg, Fred E. ..... Minneapolis
Medina, Ambrosio M., Jr. ..... Wayzata
‡ Meeker, Henry C. ..... Minneapolis
Meekin, Patrick C. ..... Minneapolis
‡ Melichar, Paul J. ..... Minneapolis
Meller, Robert L. ..... Minneapolis
Mensheha, Nicholas M. ..... Minneapolis
‡ Merner Thomas B. ..... Minneapolis
† Merrick, Charlotte T. ..... St. Paul
Merrill, Daniel C. ..... Minneapolis
Messenheimer, Myron G. ..... Minneapolis
‡ Metz, Donald D. ..... Minneapolis
Meyer, Alvin J. ..... Minneapolis
Michael, Alfred F. ..... Minneapolis
† Michael, Joseph C. ..... Pompano Beach, FL
† Michel, Henry H. ..... Minneapolis
† Michelson, Henry E. ..... Minneapolis
† Mickelson, Emma F (Fronk) ..... Holmes Beach, FL
Middlebrook, John E. ..... Minneapolis
Miller, Gerald J. ..... Ft. Riley, KS
‡ Miller, H. Dawes ..... Minneapolis
‡ Miller, Harold E. ..... Minneapolis
‡ Miller, Hugo E. ..... Minneapolis
‡ Miller, J. Carleton ..... Minneapolis
Miller, William P. ..... Minneapolis
‡ Millett, D. Keith ..... Minneapolis
‡ Minder, John G. ..... Minneapolis
Mindrum, Gerald G. ..... Minneapolis
Minsky, Armen A. ..... Minneapolis
‡ Mitby, Irvin L. ..... Minneapolis
‡ Mitchell, Berton D. ..... Minneapolis
Mitchell, Edward C. ..... College Place, WA
‡ Mitchell, Mancel T. ..... Minneapolis
‡ Mixer, Harry W. ..... Minneapolis
Moe, John H. ..... Minneapolis
†‡ Moe, W. Wyatt ..... Minneapolis
‡ Moehn, John T. ..... Minneapolis
Moen, Johannes K. ..... Minneapolis
Moghaddam, Alaeddin ..... Minneapolis
‡ Monson, Einer M. ..... Minneapolis
Monson, Paul S. ..... Minneapolis
Monson, Warren A. ..... Minneapolis
‡ Moody, David L. ..... Minneapolis
† Moore, Irvin H. ..... Eden Prairie
Moorhead, Marie ..... Minneapolis
‡ Moos, Daniel J. ..... Minneapolis
‡ Moral, Harvey M. ..... Minneapolis
Moran, Leo J. ..... New Brighton
Moriarty, James A. ..... Minneapolis
Moriarty, Joseph D. ..... Coon Rapids
Mork, A. Harold ..... Anoka
‡ Mork, Frank E. ..... Anoka
‡ Mork, Frank E., Jr. ..... Minneapolis
* Morrison, Charlotte J. ..... Minneapolis
Moss, Nyel H. ..... Minneapolis

Hennepin County Medical Society *(Continued)*

‡ Mosser, Donn G. ..... Minneapolis
‡ Moyer, Leonard B. ..... Minneapolis
‡ Mueller, James M. ..... Minneapolis
‡ Mulholland, William M. ..... Minneapolis
‡ Mullin, Gerald T., Jr. ..... Minneapolis
‡ Mulvahill, John E. ..... Minneapolis
‡ Munkittrick, Ronald C. ..... Minneapolis
Murray, Elisabeth M. ..... Minneapolis
Murphy, William R. C. ..... Minneapolis
‡ Muschenheim, Frederick ..... Minneapolis
‡ Muske, Marvin M. ..... Minneapolis
‡ Musty, Nicholas J. ..... Minneapolis
Myers, Jay A. ..... Minneapolis
‡ Myhre, James ..... Minneapolis
Mylrea, Murray J. ..... Burnsville
Nagobads, Ilgvars J. ..... Minneapolis
Nagobads, V. George ..... Minneapolis
‡ Najarian, John S. ..... Minneapolis
Nash, Eldore B. ..... Minneapolis
†‡ Neal, Joe M. ..... Minneapolis
‡ Neary, Richard P. ..... Minneapolis
† Nelson, Bernice A. ..... Minneapolis
Nelson, C. Barton ..... Minneapolis
Nelson, Carleton A. ..... Minneapolis
† Nelson, David W. ..... Minneapolis
‡ Nelson, Edward N. ..... Minneapolis
Nelson, Evan L., Jr. ..... Minneapolis
Nelson, George E. ..... Minneapolis
‡ Nelson, Glen D. ..... Minneapolis
‡ Nelson, Gunard A. ..... Minneapolis
† Nelson, Harvey ..... Deerfield Beach, FL
‡ Nelson, Lloyd S. ..... Minneapolis
Nelson, Maxine O. ..... Minneapolis
‡ Nelson, Maynard C. ..... Minneapolis
‡ Nelson, O. L. Norman ..... Minneapolis
‡ Nelson, Wallace I. ..... Minneapolis
Nerenberg, Sidney ..... Minneapolis
‡ Nesset, Lawren B. ..... Minneapolis
‡ Nesset, William D. ..... Minneapolis
Neumann, Roland F. ..... Minneapolis
‡ Neumeister, Charles A. ..... Minneapolis
Neuwirth, Gerardo D. ..... Golden Valley
Nicholas, S. Scott, Jr. ..... Minneapolis
Nicolette, Charles C. ..... Minneapolis
Nielsen, David J. ..... Minneapolis
‡ Nilsen, John A. ..... Minneapolis
Nolan, Robert K. ..... Brooklyn Center
‡ Noran, Harold H. ..... Minneapolis
‡ Nord, Robert E. ..... Minneapolis
† Nordlie, Paul E. ..... Minneapolis
‡ Noren, George R. ..... Minneapolis
‡ Norman, Franklin C. ..... Minneapolis
‡ Norman, Mark L., Jr. ..... Minneapolis
Norval, Mildred A. ..... Minneapolis
‡ Nuessle, William F. ..... Minneapolis
‡ Nydahl, Bruce C. ..... Minneapolis
‡ Nydahl, Malvin J. ..... Minneapolis
‡ O'Brien, Bruce J. ..... Minneapolis
‡ O'Brien, William A. ..... Minneapolis
† O'Donnell, James E. ..... Minneapolis
O'Neil, Bernerd L. ..... Minneapolis
‡ O'Phelan, E. Harvey ..... Minneapolis
Officer, Charles D. ..... Burnsville
‡ Ohmann, Ronald J. ..... Minneapolis
Olavs, Olga ..... Minneapolis
‡ Olfelt, Paul C. ..... Minneapolis
† Olsen, E. George ..... Minnetonka
Olsen, Jay R. ..... Minneapolis
‡ Olson, Alton C. ..... Minneapolis
Olson, C. Kent ..... Minneapolis
Olson, Carl J. ..... Minneapolis
‡ Olson, Detlof, M. ..... Minneapolis
‡ Olson, Duane C. ..... Minneapolis
Olson, Hardin E. ..... Minneapolis
† Olson, Olof A. ..... Minneapolis
‡ Olson, Philip A. ..... Minneapolis
‡ Olson, Robert A. ..... Minneapolis
Olson, Robert E. ..... Minneapolis
Olson, Robert W. ..... Minneapolis
Olson, Rolland A. ..... Wayzata
Onstad, Gerald R. ..... Minneapolis
‡ Opheim, Richard H. ..... Minneapolis
‡ Oppen, E. Gerhard ..... Minneapolis
Oppen, Melvin G. ..... Minnetonka
Opstad, Earl T. ..... Minneapolis
‡ Orbuch, Martin W. ..... Minneapolis
‡ Orkin, Milton ..... Minneapolis
Orn, Duane L. ..... Minneapolis
Osterberg, Kenneth A. ..... Minneapolis
Ostrov, Charles S. ..... Minneapolis
Ott, Eugene C. ..... Minneapolis
†‡ Overby, Philip G. ..... Minneapolis
Owen, Richard R. ..... Minneapolis
Paal, Dwain J. ..... Minneapolis
† Page, Raymond L. ..... St. Paul
‡ Paisner, Hyman M. ..... Minneapolis
Palen, Benjamin J. ..... Scottsdale, AZ
‡ Palm, E. Theodore ..... Minneapolis
‡ Paparella, Michael M. ..... Minneapolis
Papermaster, Ralph ..... Minneapolis
Papermaster, Theodore C. ..... St. Louis Park
Park, Wilford E. ..... Minneapolis
Parod, John D. ..... Minneapolis
‡ Parrott, John C. ..... Minneapolis
Pattee, James J. ..... Minneapolis
‡ Patterson, Paul G. ..... Minneapolis
Paule, William J. ..... Minneapolis
Peiper, Warren S. ..... Minneapolis
‡ Peluso, Charles R. ..... Minneapolis
Pennington, Mary ..... Minneapolis
‡ Peper, Martin C. ..... Minneapolis
‡ Perlman, Everett C. ..... Minneapolis
Perlman, Herschel L. ..... St. Louis Park
‡ Peteler, Jennings C. L. ..... Minneapolis
Petersen, Byron D. ..... Minneapolis
‡ Petersen, Deane A. ..... Minneapolis
‡ Petersen, Glenn L. ..... Minneapolis
‡ Petersen, William E. ..... Minneapolis
Peterson, Charles A. ..... Minneapolis
‡ Peterson, Charles R. ..... Minneapolis
Peterson, John A. ..... Minneapolis
‡ Peterson, Oliver H., Jr. ..... Minneapolis
Peterson, Palmer A. ..... Minneapolis
Peterson, Rodney H. ..... Minneapolis
‡ Peterson, Theodore A. ..... Minneapolis
*† Peterson, Williard C., Sr. ..... Minneapolis
‡ Peterson, Willard C., Jr. ..... Minneapolis
‡ Petit, Julien V. ..... Minneapolis
†‡ Petit, Leon J. ..... Minneapolis
‡ Pewters, John T. ..... Minneapolis
‡ Pfohl, Richard A. ..... Minneapolis
† Phelps, Kenneth A. ..... Palo Alto, CA
Phelps, Robert D. ..... Minneapolis
Phibbs, Clifford M., Jr. ..... Minneapolis
‡ Pilling, Loran F. ..... Minneapolis
Pincus, Mitchell ..... Minneapolis
Pinell, Octavio C. ..... Minneapolis
‡ Pizarro, Remi L. ..... Minneapolis

Continued on Next Page

Hennepin County Medical Society *(Continued)*

‡ Plasha, Matthew K. ..... Coon Rapids
‡ Plass, Herbert F. R. ..... Minneapolis
Pleissner, Karl W. ..... Minneapolis
Plimpton, Nathan C. ..... Minneapolis
Pohl, John F. ..... Minneapolis
† Poland, Jerome D. ..... Minneapolis
Polesky, Herbert F. ..... Minneapolis
Poley, Brooks J. ..... Minneapolis
Pollak, Kurt ..... Minneapolis
‡ Pollock, Anthony J. ..... Minneapolis
†‡ Polzak, James A. ..... Roseville
Pone, John J. ..... Minneapolis
‡ Popadiuk, Peter ..... Minneapolis
‡ Popowich, John G. ..... Minneapolis
† Poppe, Frederick H. ..... Miami, FL
Potter, Robert B. ..... Minneapolis
Pratt, Fred J. ..... Minneapolis
‡ Prem, Konald A. ..... Minneapolis
‡ Preston, Frank S., Jr. ..... Minneapolis
‡ Price, William E. ..... Minneapolis
‡ Prickman, William E. ..... Minneapolis
‡ Priest, Robert E. ..... Minneapolis
*† Prim, Joseph A. ..... Minneapolis
Proshek, Lumir C. ..... Minneapolis
‡ Quello, Robert O. B. ..... Minneapolis
Quiggle, Arthur B. ..... Minneapolis
‡ Quist, Henry W., Jr. ..... Minneapolis
Raab, David E. ..... Minneapolis
Racer, Harley J. ..... Minneapolis
Raich, John J. ..... Minneapolis
‡ Raile, Richard B. ..... Minneapolis
Randall, David A. ..... Minneapolis
‡ Ransom, H. Robert ..... Osseo
‡ Ratelle, Alexander E. ..... Minneapolis
Recht, Thomas M. ..... Minneapolis
‡ Reece, Richard L. ..... Minneapolis
Reed, Sheldon C. ..... Minneapolis
Regan, John J. ..... Minneapolis
*†‡ Regnier, Edward A. ..... Minneapolis
Rehmann, Ronald E. ..... Coon Rapids
Reichel, Samuel M. ..... Minneapolis
‡ Reif, Harold A. ..... Minneapolis
‡ Reiley, Richard E. ..... Minneapolis
‡ Reinhart, Richard O. ..... Minneapolis
‡ Reisdorf, George E. ..... St. Louis Park
‡ Reiser, Milton P. ..... Minneapolis
† Reller, Carl Raymond, Jr. ..... Minneapolis
‡ Remole, William D. ..... Minneapolis
‡ Remsberg, John R. S. ..... Springfield, MA
‡ Resch, Joseph A. ..... Minneapolis
Reynolds, James ..... Minneapolis
Rholl, Arnold O. ..... Minneapolis
‡ Rice, Carl O. ..... Minneapolis
Rice, Edwin G. ..... Minneapolis
Rice, Fred A. ..... Minneapolis
‡ Richardson, Robert J. ..... Minneapolis
†‡ Richdorf, Lawrence F. ..... Minneapolis
‡ Rierson, Phillip A. ..... Minneapolis
Riley, John D. ..... Minneapolis
Riordan, Elsie M. ..... Minneapolis
‡ Ripple, Rudolph J., Jr. ..... Minneapolis
‡ Risch, Ronald E. ..... Minneapolis
Rizer, Dean K. ..... Minneapolis
† Robb, Edwin F. ..... Boca Raton, FL
‡ Robbins, Owen F. ..... Minneapolis
Roberts, Byron H. ..... Minneapolis
‡ Roberts, Lewis J. ..... Minneapolis
Robinson, Cortland O. ..... Minneapolis
‡ Rock, William H. ..... Anoka
‡ Rocknem, Robert E. ..... Minneapolis
Rockwell, Curtiss V. ..... Minneapolis
‡ Rodgers, Richard S. ..... Minneapolis
Rogin, Norton ..... Minneapolis
Rollins, Pat ..... Minnetonka
Romness, Kenneth B. ..... Mound
‡ Rosenbaum, David L. ..... Minneapolis
‡ Rosendahl, Frederick G. ..... Minneapolis
† Rosenfield, Abraham B. ..... Minneapolis
Rosenow, John H. ..... Minneapolis
† Rosenquist, Rudolph J. ..... Minneapolis
† Rosenstein, Hanan J. ..... Minneapolis
†‡ Rosenwald, Reuben M. ..... Anoka
‡ Rossen, Ralph ..... Minneapolis
Rotenberg, Robert J. ..... Minneapolis
Rotenberg, Samuel ..... Beverly Hills, CA
‡ Rothnem, Morris S. ..... Minneapolis
Rubin, Manly ..... Minneapolis
Rucker, Thomas K. ..... Minneapolis
† Rucker, William H. ..... Minneapolis
† Rud, Norman E. ..... Edina
‡ Ruiz, Ernest ..... Minneapolis
‡ Russeth, Arthur N. ..... Minneapolis
‡ Rusten, Elmer M. ..... Minneapolis
Rydberg, John S. ..... Minneapolis
* Rydburg, Wayne C. ..... Minneapolis
Rydland, Arne D. ..... Minneapolis
St. Cyr, Harry M. ..... Minneapolis
St. Cyr, Kenneth J. ..... Minneapolis
‡ Salchert, John J. ..... Minneapolis
‡ Salovich, Edward L. ..... Minneapolis
‡ Salovich, Elmer R. ..... Minneapolis
‡ Sanchez, Jose S. ..... Edina
‡ Sandt, Karl E. ..... La Jolla, CA
‡ Sanfilippo, Sylvester J. ..... Minneapolis
Sartor, Richard ..... Minneapolis
Sawyer, Glen T. ..... Minneapolis
Saythe, Keith D. ..... Minneapolis
‡ Sborov, Abe M. ..... Minneapolis
Scallen, Raymond W. ..... Minneapolis
‡ Scanlan, Patrick J. ..... Minneapolis
Schaar, Frances E. ..... Minneapolis
Schaefer, Wesley G. ..... Minneapolis
Schaffhausen, Irwin F. ..... Minneapolis
Schaffhausen, Mildred ..... Minneapolis
‡ Scherer, L. Raymond ..... Minneapolis
Scherling, Sidney S. ..... Minneapolis
Schiele, Burtrum C. ..... Minneapolis
Schissel, Gregory A. ..... Minneapolis
‡ Schissel, Richard C. ..... Minneapolis
Schmidt, W. Robert ..... Minneapolis
† Schmitt, Samuel C. ..... Fallbrook, CA
Schneck, Jack I. ..... Minneapolis
Schoening, Herbert A. ..... Minneapolis
Schoenwetter, William F. ..... Minneapolis
‡ Schottler, Jerry L. ..... Minneapolis
Schottler, Max E. ..... Minneapolis
†‡ Schroeder, Albert J. ..... Minneapolis
‡ Schultz, Alan ..... Minneapolis
‡ Schultz, Alvin L. ..... Minneapolis
‡ Schultz, J. Harold ..... Minneapolis
‡ Schultz, Peter J. ..... Minneapolis
Schultz, Robert J. ..... Minneapolis
‡ Schulze, William M. ..... Minneapolis
‡ Schumacher, John W. ..... Minneapolis
Schumacher, Robert V. ..... Minneapolis
‡ Schut, Lawrence J. ..... Minneapolis
Schwartz, E. Robert ..... Minneapolis
‡ Scott, Horace G. ..... Minneapolis
‡ Scott, Robert H. ..... Minneapolis

Hennepin County Medical Society *(Continued)*

Scott, William R. ....Minneapolis
† Seaberg, John A. ....Pequot Lakes
Seay, James E., III ....Minneapolis
Segal, Edward L. ....Minneapolis
Segal, Martin A. ....Minneapolis
Segal, Marvin S. ....Minneapolis
‡ Segal, Sheldon J. ....Minneapolis
† Seham, Max ....St. Paul
Seifert, Gregory L. ....Minneapolis
† Seifert, Milton H. ....Excelsior
‡ Seifert, Milton H., Jr. ....Excelsior
‡ Seljeskog, Edward L. ....Minneapolis
Semba, Thomas ....Minneapolis
‡ Semsch, Robert D. ....Wayzata
Severseike, Odean M. ....Minneapolis
‡ Seymour, John L. ....Minneapolis
Shackelford, Terry C. ....Minneapolis
‡ Shandorf, James F. ....Minneapolis
Shackelford, Terry C. ....Minneapolis
† Shaperman, Eva P. ....La Mesa, CA
‡ Shapiro, Fred L. ....Minneapolis
Shapiro, Irving ....Minneapolis
Shapiro, Sidney K. ....Minneapolis
‡ Shapiro, Stanley W. ....Minneapolis
‡ Shattuck, Clark A. ....Minneapolis
‡ Shaw, Howard A. ....Minneapolis
Shea, Andrew W. ....Minneapolis
‡ Shemesh, Alvin ....Minneapolis
‡ Sher, Lewis ....Minneapolis
‡ Sherman, Lloyd F. ....Minneapolis
† Shillington, Maurice A. ....Ft. Lauderdale, FL
Sholler, Lawrence J. ....Minneapolis
Shragg, Robert I. ....Minneapolis
Shronts, John F. ....Minneapolis
Sidell, Franklin D. ....Minneapolis
Siegmann, William C. ....Minneapolis
‡ Sigel, Melvin E. ....Minneapolis
‡ Silas, Ralph M. ....Minneapolis
Silver, John D. ....Minneapolis
‡ Silverstein, Paul M. ....Minneapolis
‡ Simmons, Richard K. ....Minneapolis
Simmons, Richard L. ....Minneapolis
Simo, Kathleen Kay ....Minneapolis
‡ Simonson, Donald B. ....Minneapolis
Singher, Lawrence J. ....Minneapolis
‡ Sinykin, Melvin B. ....Minneapolis
Sipe, James W. ....Coon Rapids
‡ Skjold, Arthur C. ....Minneapolis
‡ Sletten, Richard G. ....Minneapolis
‡ Slosser, Gaius, J., II ....Minneapolis
Smiley, John T. ....Minneapolis
†‡ Smisek, Frank M. ....Minneapolis
† Smith, Adam M. ....Minneapolis
‡ Smith, Archie M. ....Minneapolis
Smith, Barlow ....Minneapolis
‡ Smith, Baxter A., Jr. ....Minneapolis
‡ Smith, Graham G. ....Minneapolis
Smith, Henry T. ....Minneapolis
‡ Smith, John E. ....Minneapolis
Smith, Nadine G. ....Minneapolis
‡ Smith, Theodore S. ....Minneapolis
‡ Soderberg, Richard J. ....Minneapolis
†‡ Soderlind, Ragnar T. ....Minneapolis
‡ Soiseth, Robert P. ....Minneapolis
‡ Solhaug, Samuel B., Jr. ....Minneapolis
Solvason, Harold M. ....Minneapolis
‡ Spano, Joseph P. ....Minneapolis
‡ Spencer, Bernard J. ....Minneapolis
† Spencer, David L. ....Anoka
Spink, Wesley W. ....Minneapolis
‡ Sponsel, Kenath H. ....Minneapolis
‡ Stahr, Aubrey C. ....Hopkins
Standefer, James E. ....Minneapolis
† Stanford, Charles E. ....Elcho, WI
*† Stanley, Court R. ....Minneapolis
‡ Steidl, Richard M. ....Minneapolis
†‡ Stelter, Lloyd A. ....Minneapolis
† Stenstrom, Annette T. ....Grand Marais
Stenzel, Donald A. ....Minneapolis
Stenzel, Joseph A. ....Minneapolis
Stephens, William E. ....Minneapolis
Sterrie, Norman A. ....Minneapolis
Stevens, Sheridan S. H. ....Minneapolis
‡ Stewart, Marvin J. ....Minneapolis
Stewart, Paul B. ....Minneapolis
‡ Stiegler, Farrell S. ....Minneapolis
‡ Stillman, M. Thomas ....Minneapolis
Stolee, Curtis N. ..Republique Malgeche, Madagascar
‡ Stoltz, Robert C. ....Minneapolis
‡ Stone, Norman F. ....Minneapolis
Stone, Stanley P. ....Minneapolis
Strait, Herbert S. ....Minneapolis
‡ Strand, Clarence M. ....Minneapolis
‡ Strand, Peter J. ....Minneapolis
‡ Streu, Richard E. ....Minneapolis
‡ Strickler, Jacob H. ....Minneapolis
Strobel, Jack L. ....Minneapolis
‡ Strom, Gordon W. ....Minneapolis
‡ Strom, Robert L. ....Minneapolis
‡ Stromgren, Delph T. ....Minneapolis
Stromme, William B. ....Minneapolis
Strunk, Clarence A. ....Minneapolis
‡ Student, Richard E. ....Minneapolis
‡ Sturges, Robert L. ....Minneapolis
Subak, Barbara H. ....Minneapolis
‡ Subby, Walter ....Minneapolis
Sukov, Marvin ....Minneapolis
‡ Sulciner, Aurel ....Minnetonka
‡ Sundberg, A. Bruce ....Minneapolis
‡ Sutherland, John E. ....Minneapolis
Swaiman, Kenneth F. ....Minneapolis
‡ Swallen, Thomas O. ....Minneapolis
†‡ Swanson, David A. ....Minneapolis
Swanson, Gerald E. ....Minneapolis
‡ Swanson, John O. ....Minneapolis
†‡ Sweetser, Horatio B. ....Minneapolis
‡ Sweetser, Theodore H., Jr. ....Minneapolis
‡ Swendseen, Carl J. ....Minneapolis
Swenson, James D. ....Minneapolis
‡ Swenson, Richard W. ....Minneapolis
Swift, Dean C. ....Minneapolis
Symchych, Boris E. ....Minneapolis
‡ Tam, Ernest C. ....Minneapolis
‡ Tambornino, Joseph M. ....Minneapolis
Tanaka, Shin ....Minneapolis
‡ Tangen, George V. ....Minneapolis
† Taylor, Joseph H. ....Ft. Lauderdale, FL
‡ Tchou, Mien-Fa ....Minneapolis
‡ Telander, Robert L. ....Minneapolis
tenBensel, Robert W. ....Minneapolis
‡ Tenner, Robert J. ....Minneapolis
‡ Teska, Byron A. ....Minneapolis
‡ Teynor, Joseph W. ....Minneapolis
‡ Tharp, Ralph ....Minneapolis
Thelemann, Arthur R., Jr. ....Minneapolis
Theobalt, Inge M. ....Minneapolis
‡ Theologides, Anthanasios ....Minneapolis
Thomas, William H. ....Minnetonka

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Hennepin County Medical Society *(Continued)*

Thomasson, Robert D. ....Minneapolis
Thomes, A. Boyd ....Minneapolis
Thompson, Arthur ....Minneapolis
‡ Thorson, Stuart V. ....Minneapolis
Thysell, Desmond M. ....Minneapolis
Titrud, Leonard A. ....Minneapolis
‡ Tobin, John A. ....Minneapolis
Tobin, John D. ....Minneapolis
‡ Torp, William B. ....Minneapolis
Torres, Fernando ....Minneapolis
† Town, Louise A. ....Minneapolis
Townes, C. Dwight, Jr. ....Minneapolis
Trach, Benedict B. ....Minneapolis
Treat, William A. ....Minneapolis
Trost, Francis J. ....Minneapolis
‡ Trow, James E. ....Minneapolis
Tsai, Shih Hao ....Minnetonka
‡ Tucker, Richard C. ....Minneapolis
‡ Tudor, Richard B. ....Minneapolis
Turbak, Charles E. ....Minneapolis
‡ Turkbas, Nejat ....St. Paul
‡ Twidwell, Joseph E. ....Minneapolis
Ulrich, Wesley D. ....Bethesda, MD
‡ Ulvestad, Harold S. ....Minneapolis
‡ Utendorfer, Robert W. ....Minneapolis
‡ Vaaler, Robert T. ....Minneapolis
‡ Valgemae, Romil ....Minneapolis
Van Oppen, Dirk J. A. ....Minneapolis
Vellek, Donald G. ....Minneapolis
Vennes, Jack A. ....Minneapolis
Vik, A. Elliott ....Minneapolis
Vilaseca, Louis B. ....Minneapolis
‡ Von Drashek, Stanley C. ....Minneapolis
von Weiss, David L. ....Minneapolis
Vorlicky, Loren N. ....Minneapolis
Wagner, Christian J. ....Minneapolis
‡ Wagner, Robert M. ....Minneapolis
† Waldron, Carl W. ....Scottsdale, AZ
‡ Waldron, John F. ....Minneapolis
Walker, Frederick E., Jr. ....Minneapolis
Wall, Carl R. ....Minneapolis
‡ Wallinga, Jack V. ....Minneapolis
† Walonick, Albert L. ....Hopkins
Walsh, John G. ....Minneapolis
Wang, Josef K. ....Minneapolis
† Wangensteen, Owen H. ....Minneapolis
Ward, A. Neal ....Minneapolis
‡ Warren, John W. ....Minneapolis
Watson, C. Gordon ....Minneapolis
Watson, Cecil J. ....Minneapolis
Wattenberg, Lee W. ....Minneapolis
‡ Weatherhead, D. Stuart P. ....Minneapolis
‡ Webb, Edgar A. ....Minneapolis
‡ Webber, Richard J. ....Minneapolis
‡ Weber, Lowell W. ....Minneapolis
Weisberg, Martin G. ....Minneapolis
Weisberg, Rapheal J. ....Minneapolis
Weisel, Mary R. ....Minneapolis
‡ Wendland, John P. ....Minneapolis
Wengler, Robert A. ....Minneapolis
† Werges, Thomas M. ....Minneapolis
Werner, George ....Minneapolis
‡ Wesolowski, Stanley ....Minneapolis
† West, Catherine C. ....Edina
Wester, Mary Sue ....Minneapolis
Westgate, Hugh D. ....Minnetonka
† Wetherby, Macnider ....Minneapolis
Wethington, Joseph F. ....Coon Rapids
‡ Wett, Richard J. ....Minneapolis
Wexler, Harold M. ....Minneapolis
‡ Wheeler, Robert W. ....Minneapolis
Whitacre, John C., II ....Minneapolis
White, Asher A. ....Minneapolis
† White, Willard D. ....Edina
Whitesell, Lloyd A. ....Minneapolis
‡ Widen, Wilford F. ....Minneapolis
‡ Wigdahl, Luther O. ....Minneapolis
Wigg, Norman P. ....Minneapolis
‡ Wilcox, William A. ....Minneapolis
Wild, John J. ....Minneapolis
† Wilder, Kenneth W. ....Minneapolis
† Wilder, Robert L. ....Minneapolis
† Wilder, Russell M., Jr. ....Topeka, KS
‡ Wilder, Walter L. ....Minneapolis
†‡ Wilken, Paul A. ....Minneapolis
†‡ Williams, Henry L. ....West St. Paul
‡ Williams, Paul A. ....Minneapolis
Williams, Richard E. ....Robbinsdale
Wilson, John A. ....Minneapolis
‡ Wilson, Robert E. ....Minneapolis
‡ Wilson, Thomas M., Jr. ....Minneapolis
Winchell, Paul ....Minneapolis
† Winther, Nora M. C. ....Columbus, OH
‡ Wippermann, Frederic F. ....Minneapolis
‡ Wisiol, Erich S. ....Minneapolis
Wisness, Osmund A. ....Savage
Woellner, Richard C. ....Minneapolis
†‡ Wohlrabe, Arthur A. ....Minneapolis
‡ Wohlrabe, A. Cabot ....Minneapolis
‡ Wohlrabe, Robert G. ....Minneapolis
‡ Wolter, Frederick H. ....Minneapolis
Wong, Edward T. ....Minneapolis
Woodley, Donald W. ....Minneapolis
Woodbury, John W. ....Minneapolis
‡ Worrell, Philip J. ....Minneapolis
‡ Woyda, William C. ....Minneapolis
Wright, Donald L. ....Minneapolis
‡ Wright, Francis S. ....Minneapolis
Wright, William S. ....Minneapolis
Wuest, Frederick C. ....Wayzata
† Wynne, Herbert M. N. ....Wayland, MA
‡ Yeager, Terrell F. ....Anoka
Yelle, Matthew D. ....Anoka
†‡ Ylvisaker, Ragnvald S. ....Minneapolis
Yonehiro, Earl G. ....Minneapolis
Young, Ronald C. ....Minneapolis
Yue, Wen Y. ....Excelsior
Zahrendt, O. Lewis ....Minneapolis
Zak, Solomon J. ....Minneapolis
‡ Zarling, V. Richard ....Minneapolis
‡ Zaworski, Leo A. ....Minneapolis
‡ Zelickson, Alvin S. ....Minneapolis
Zemmers, Robert M. ....Ft. Lewis, WA
† Zierold, Arthur A. ....Minneapolis
‡ Zinn, Charles W. ....Wayzata
‡ Zinter, Ferdinand A. ....Minneapolis

KANDIYOHI-SWIFT-MEEKER COUNTY MEDICAL SOCIETY

Kandiyohi, Swift and Meeker Counties
Regular meetings, third Thursday of each month
Annual meeting in November
Number of members 59

PRESIDENT
Griffin, Richard P. ..... Willmar
SECRETARY
Eichelberger, Dale ..... Willmar

‡ Allison, David D. ..... Litchfield
† Anderson, Richard E. ..... Willmar
Bosland, Howard G. ..... Rochester
Chunn, Stanley S. ..... Willmar
Danielson, Lennox ..... Litchfield
Dille, Donald E. ..... Litchfield
Docksey, John W. ..... Willmar
Dreyling, Roger A. ..... Eden Valley
Dunstan, Paul L. ..... Willmar
Eberley, Tobe S. ..... Benson
Eichelberger, Dale L. ..... Willmar
Ellinger, Albert J. ..... Willmar
Fedders, Skaidrite ..... Willmar
Fedor, Robert D. ..... Willmar
† Frederickson, Alice C. ..... Willmar
Gaebe, Milton B. ..... Clara City
† Giere, Silas W. ..... Benson
Gilman, Lloyd C. ..... Willmar
Griffin, Richard P. ..... Benson
Guy, Jack A. ..... New London
Hazen, Richard W. ..... Willmar
Hinderaker, Harris P. ..... Willmar
Hinz, Walter E. ..... Willmar
Hodapp, Robert V. ..... Willmar
Houts, Joseph C. ..... Dassel
Jacobs, Douglas L. ..... Willmar
Johnson, Daniel A. ..... Litchfield
Johnson, Marvin W. ..... Dassel
Kaufman, Edward J. ..... Appleton
Larrabee, Walter F., Jr. ..... Willmar
Leitch, Cecil ..... Litchfield
McAfee, David K. ..... Willmar
McCarthy, Austin M. ..... Willmar
† Macklin, William E. ..... Litchfield
Maitland, Edwin T. ..... Willmar
Malone, Patrick M. ..... Willmar
Mattson, Donald S. ..... Willmar
Meinert, John K. ..... Willmar
Michels, Roger P. ..... Willmar
Munneke, Lyle ..... Clara City
Nelson, Robert H. ..... Benson
Nolan, William ..... Litchfield
Olson, Gregory M. ..... Litchfield
Opsahl, Lawrence J. ..... Willmar
Petersen, Donald H. ..... Willmar
Peterson, Willard ..... Willmar
‡ Proeschel, Ray K. ..... Willmar
Rorem, Joseph A. ..... Appleton
Ruchie, Warren H. ..... Willmar
Ruhe, Albert ..... Willmar
Rygh, Harold N. ..... Atwater
Sadd, Milton ..... Willmar
Salter, William M. ..... Willmar
Schnell, Frederick S. ..... Litchfield
Skaife, William F. ..... Benson
Smith, Lloyd A. ..... Willmar
Strand, Roger W. ..... Willmar
Thompson, Robert R. ..... Willmar
‡ Thompson, Russell A. ..... Willmar
‡ Wagner, Norman W. ..... Benson
Wilmot, Cecil A. ..... Litchfield
† Wilmot, Harold E. ..... Litchfield

LYON-LINCOLN COUNTY MEDICAL SOCIETY

Lyon and Lincoln Counties
Refular meetings, 6 meetings—Spring and Fall
Annual meeting, November
Number of members 26

PRESIDENT
Odland, O. M. ..... Marshall
SECRETARY
Stover, Laddie E. ..... Marshall

‡ Bosley, Patrick ..... Balaton
‡ Eckdale, John E. ..... Marshall
†‡ Ford, Burton C. ..... Marshall
‡ Hedenstrom, Philip C. ..... Marshall
‡ Johnson, C. Percy ..... Tyler
Johnston, Bemis H. ..... Eatontown, NJ
Kaczrowski, William ..... Marshall
† Kreuzer, Titus C. ..... Ft. Snelling
‡ Lee, Norman J. ..... Tracy
‡ Monson, Leonard J. ..... Canby
‡ Mueller, LeRoy E. ..... Hendricks
‡ Muesing, Mark A. ..... Tyler
‡ Mulder, Richard D. ..... Marshall
‡ Murphy, Joseph E. ..... Marshall
‡ Myers, John W. ..... Canby
‡ Odland, Olin M. ..... Marshall
‡ Olson, Robert T. ..... Canby
Panning, Wayne P. ..... Marshall
‡ Peterson, Kenneth A. ..... Marshall
† Rohrer, Christian A. ..... Madison Lake
Schroeppel, Roger ..... Tracy
‡ Stover, Laddie E. ..... Marshall
‡ Taintor, Ronald W. ..... Marshall
‡ Thompson, Carl O. ..... Hendricks
† Workman, Warner G. ..... Tracy
† Yaeger, Wilbert W. ..... Torrance, CA

McLEOD COUNTY MEDICAL SOCIETY

McLeod County
Regular meetings, third Thursday of each month
Annual meeting, November
Number of members 15

PRESIDENT
Jensen, Alvin M. ..... Brownton
SECRETARY
Selmo, Joseph D. ..... Norwood
‡ Bretzke, Carl O. ..... Hutchinson
Close, Gerald A. ..... Glencoe
‡ Griebie, Grant L. ..... Hutchinson
‡ Hegrenes, Robert L. ..... Htuchinson
‡ Huebert, Dan W. ..... Hutchinson
‡ Jensen, Alvin M. ..... Brownton
‡ Lippmann, Elmer W. ..... Hutchinson
‡ McNeil, Maurice R. ..... Glencoe
‡ Navratil, Donald R. ..... Glencoe
‡ Peterson, Kenneth H. ..... Hutchinson
‡ Selmo, Joseph D. ..... Norwood
‡ Smith, George R. ..... Hutchinson
‡ Smyth, John J. ..... Lester Prairie
‡ Stifter, A. J. ..... Winsted
‡ Truesdale, Clark W. ..... Saudi Arabia

MOWER COUNTY MEDICAL SOCIETY

Mower County
Regular meetings, last Friday of the month
Annual meeting, November
Number of members 34

PRESIDENT
Lommen, Peter, Jr. ..... Austin
SECRETARY
Todd, John C. ..... Austin
‡ Anderson, David P., Jr. ..... Austin
‡ Anderson, Harold J. ..... Austin
‡ Barber, Tracy E. ..... Austin
Elliott, Harold J. ..... Hayfield
‡ Hagen, John D. ..... Austin
† Hertel, Garfield E. ..... McAllen, TX
‡ Hesla, Inman A. ..... Austin
‡ Isele, Reginald H. ..... Austin
† Leck, Paul C. ..... Palm Desert, CA
‡ Lommen, M. L. ..... Austin
*†‡Lommen, Peter A. ..... Austin
Lommen, Peter A., Jr. ..... Austin
† McKenna, Jay K. ..... LaJolla, CA
‡ Miller, Herman ..... Austin
‡ Mlinar, Joseph P. ..... Austin
† Morse, Morton P. ..... LeRoy
Morse, Roger D. ..... LeRoy
‡ Muchow, Gene C. ..... Austin
‡ Nesse, James A. ..... Austin
‡ O'Rourke. William J. ..... Austin
‡ Pesonen, Clifford A. ..... Austin
‡ Peterson, Stanley C. ..... Austin
‡ Roberts, George A. ..... Austin
† Robertson, Paul A. ..... Austin
‡ Seery, Thomas M. ..... Austin
† Smythe, Gwendolyn S. ..... Austin
‡ Smythe, Lowell J. ..... Austin
‡ Stahl, G. W. ..... Austin
‡ Taufic, Mansur ..... Austin
† Thomson, James M. ..... Austin
‡ Todd, John C. ..... Austin
‡ Trudeau, David ..... Austin
‡ Twiggs, Leo F. ..... Austin
‡ Van Cleve, H. P., Jr. ..... Austin
‡ Wright, Robert R. ..... Austin

NICOLLET-LeSUEUR COUNTY MEDICAL SOCIETY

Nicollet and LeSueur Counties
Regular meetings, first Monday of even months
Annual meeting, December
Number of members 20

PRESIDENT
Engstrom, George ..... St. Peter
SECRETARY
Walden, A. Don ..... LeSueur
‡ Anderson, Jo E. ..... LeSueur
Brink, Donald ..... St. Peter
‡ Engstrom, George E. ..... St. Peter
‡ Grimes, Burton P. ..... St. Peter
† Haes, Julius E. ..... St. Peter
†‡ Hiniker, Peter J. ..... St. Peter
Koskela, L. E. ..... St. Peter
Larson, Milo H. ..... St. Peter
‡ Lenander, Mellvin E. L. ..... St. Peter
Olmanson, Edmund G. ..... St. Peter
‡ Olmanson, M. Donald ..... St. Peter
‡ Olmanson, Vern ..... St. Peter
Sauer, Jean C. ..... Ft. Snelling
‡ Sheppard, Charles G. ..... St. Peter
‡ Sjostrom, Lawrence E. ..... St. Peter
‡ Sonnesyn, Nels N. ..... LeSueur
‡ Strathern, Carleton S. ..... St. Peter
Thompson, A. Henry ..... St. Peter
Walden, A. Don ..... LeSueur
† Wohlrabe, Clarence F. ..... North Mankato

PARK REGION DISTRICT AND COUNTY MEDICAL SICIETY

Douglas, Grant, Otter Tail and Wilkin Counties
Regular meetings, March, June, September and December
Annual meeting, December
Number of members 60

PRESIDENT
Tanquist, Edwin ..... Alexandria
SECRETARY
Syverson, Leslie A. ..... Fergus Falls

Akhavan, Traz H. ..... Alexandria
† Arndt, Harry W. ..... Detroit Lakes
Baker, Jeannette L. ..... Fergus Falls
Baker, Norman H. ..... Fergus Falls
Bateman, Clarence V. ..... Fergus Falls
Bhattacharyya, Sisir K. ..... Battle Lake
Boline, Clifford A. ..... Battle Lake
Cain, James H. ..... Alexandria
Carlson, Carl E. ..... Alexandria
Carlson, Homer J. ..... Pelican Rapids
Colman, Edward L. ..... Fergus Falls
‡ Daehlin, Rolf ..... Fergus Falls
‡ Doms, Vernon A. ..... Elbow Lake
Emerson, Edwin E. ..... Osakis
Engebretson, Paul ..... Alexandria
‡ Estrem, Ralph L. ..... Fergus Falls
Estrem, Robert D. ..... Fergus Falls
Geiser, Peter M. ..... Alexandria
Green, John F. ..... Alexandria
Hanson, Everett C. ..... New York Mills
Heegaard, William G. ..... Alexandria
†‡ Helseth, Hovald K. ..... Fergus Falls
‡ Hom, Leong Y. W. ..... Fergus Falls
† Houkom, Bjarne ..... Fergus Falls
‡ Jacobson, Clifford W. ..... Breckenridge
‡ Kevern, Jay L. ..... Henning
‡ Kippen, Neil ..... Breckenridge
‡ Korda, Henry A. ..... Pelican Rapids
Kuhlmann, Vernon G. ..... Alexandria
Larson, Dorette W. ..... Fergus Falls
‡ Lewis, Charles W. ..... Henning
Lu, Cheng-en ..... Fergus Falls
Lu, Jennie W. G. ..... Fergus Falls
Lueders, James ..... Evansville
Luh, Edwin F. ..... Fergus Falls
† Mortensen, Nels G. ..... St. Paul
‡ Mouritsen, Glenn J. ..... Fergus Falls
Nelson, Roy A. ..... Fergus Falls
‡ Ness, Richard A. ..... Fergus Falls
‡ Nicholson, Richard W. ..... Fergus Falls
‡ O'Brien, Louis T. ..... Breckenridge
Olson, Frances P. ..... Fergus Falls
‡ Orandi, Ahmad ..... Fergus Falls
‡ Orandi, Mehdi ..... Fergus Falls
† Ostergaard, Erling ..... Elbow Lake
Perkins, Douglass E. ..... Alexandria
Pulido, Ernesto ..... Fergus Falls
Reinhardt, James H. ..... Alexandria
‡ Richter, Paul H. ..... Fergus Falls
‡ Rockwood, Philo H. ..... Fergus Falls
‡ Sanderson, David J. ..... Fergus Falls
Schoeneberger, P. B. ..... Perham
‡ Shaver, Ward ..... Fergus Falls
* Sporre, Knute A. ..... Fergus Falls
Stemsrud, Harold L. ..... Alexandria
Struthers, Lewis ..... Parkers Prairie
‡ Syverson, Leslie A. ..... Fergus Falls
† Tanquist, Edwin J. ..... Alexandria
Tanquist, Edwin J., Jr. ..... Alexandria
Undem, Dale ..... Alexandria
Warner, James J. ..... Perham
Wasson, Loren F. ..... Alexandria

RAMSEY COUNTY MEDICAL SOCIETY

Ramsey County
Regular meetings, last Monday each month except
June, July and August
Annual meeting in January
Number of members 634

PRESIDENT
Ravits, Harold G. ..... St. Paul
SECRETARY
Johnson, Herbert W. ..... St. Paul
EXECUTIVE SECRETARY
Aldean, Mrs. Sue ..... St. Paul

Abrams, Alexander, Jr. ..... St. Paul
‡ Adair, Albert F., Jr. ..... St. Paul
Adams, Harold R. ..... St. Paul
Adcock, Leon L. ..... St. Paul
Ahlstrom, Robert C. ..... St. Paul
‡ Ahrens, Robert M. ..... St. Paul
‡ Albrecht, Raymond ..... St. Paul
‡ Alden, John F. ..... St. Paul
‡ Altman, Robert L. ..... St. Paul
‡ Alton, Donald G. ..... St. Paul
‡ Amerongen, Werner W. ..... St. Paul
Anderson, Dale L. ..... St. Paul
‡ Anderson, David W. ..... St. Paul
Anderson, James J. ..... St. Paul
Anderson, Margaret C. ..... St. Paul
‡ Anderson, Richard W. ..... St. Paul
‡ Antolak, Stanley J., Jr. ..... St. Paul
Arny, Frederick D. ..... St. Paul
Arny, Frederick P. ..... St. Paul
Ashmore, Herbert C. ..... St. Paul
‡ Auran, David B. ..... St. Paul
‡ Aurelius, J. Richards ..... St. Paul
‡ Ausman, Duane R. ..... St. Paul
‡ Austrian, Sol ..... St. Paul
‡ Babb, Frank S. ..... St. Paul
Bach, Jerome M. ..... St. Paul
‡ Bah, Merle C. ..... St. Paul
‡ Baker, C. Robert, Jr. ..... St. Paul
‡ Balce, Regino V. ..... St. Paul
Bauer, Eugene L. ..... St. Paul
Bean, Samuel F. ..... St. Paul
‡ Beck, Charles J. ..... North St. Paul
Beckman, Donovan L. ..... St. Paul

Continued on Next Page

Ramsey County Medical Society *(Continued)*

‡ Beek, Harvey O. ..... St. Paul
‡ Beer, John J. ..... St. Paul
‡ Bellomo, James ..... St. Paul
Belsito, Alphonso A. ..... St. Paul
‡ Belz, Reinmar ..... St. Paul
Benthack, Elaine M. ..... Minneapolis
Bergh, Allen V. ..... St. Paul
‡ Bernier, M. J. ..... North St. Paul
† Bernstein, William C. ..... St. Paul
‡ Bieter, Thomas G. ..... St. Paul
Birkebak, Roland C. ..... St. Paul
Bjornson, Robert G. B. ..... St. Paul
† Black, Earl J. ..... White Bear Lake
Blackburn, Henry W. ..... St. Paul
‡ Blomberg, William R. ..... St. Paul
Blumberg, Henry B. ..... St. Paul
† Bock, Rolland A. ..... St. Paul
Boies, Lawrence R., Jr. ..... St. Paul
Bonello, Frank J. ..... St. Paul
† Bouma, Lewis R. ..... St. Paul
‡ Brainard, John B. ..... St. Paul
Breen, John J. ..... St. Paul
Briggs, John F. ..... St. Paul
‡ Briggs, Thomas G. ..... White Bear Lake
† Brockberg, Daryl G. ..... St. Paul
† Brockberg, James A. ..... St. Paul
Broadie, Thomas E. ..... St. Paul
†‡ Brodie, Walter D. ..... St. Paul
‡ Broman, Harold R., Jr. ..... North St. Paul
Brown, Charles T. ..... St. Paul
‡ Brown, Christopher J. ..... Mineral Wells, TX
‡ Brown, Hector M. ..... St. Paul
Brown, James E. ..... St. Paul
‡ Brown, James P. ..... St. Paul
‡ Brown, John M. ..... St. Paul
‡ Bruhl, Martin G. ..... St. Paul
‡ Bulinski, Theodore J. ..... St. Paul
‡ Burklund, Edwin C. ..... St. Paul
Burlingame, David A. ..... St. Paul
‡ Burmeister, Richard O. ..... St. Paul
‡ Burns, John M. ..... St. Paul
‡ Burton, J. Richard ..... St. Paul
‡ Bush, Robert P. ..... St. Paul
Butwinick, Conrad S. ..... St. Paul
‡ Byrne, William J. ..... St. Paul
‡ Cain, Clark L. ..... St. Paul
Capistrant, Terrance D. ..... St. Paul
‡ Carey, Lewis S. ..... St. Paul
‡ Carley, Richard B. ..... St. Paul
Castle, Donald D. ..... St. Paul
‡ Cass, Alexander S. ..... St. Paul
Cedarleaf, Cherry B. ..... White Bear Lake
† Chatterton, Carl C. ..... St. Paul
† Cich, John A. ..... West Saint Paul
‡ Clark, W. Bruce ..... St. Paul
Cleary, John ..... St. Paul
‡ Cochrane, Byron B. ..... St. Paul
Coddon, Walter D. ..... St. Paul
†‡ Colby, Woodward L. ..... St. Paul
Cole, Wallace H. ..... St. Paul
‡ Coleman, John B. ..... St. Paul
‡ Colton, Roger S. ..... St. Paul
‡ Comfort, Thomas H. ..... Minneapolis
‡ Connolly, Coleman J. ..... St. Paul
‡ Connolly, Joseph P. ..... South St. Paul
† Connor, Charles E. ..... St. Paul
Cooper, Charles C. ..... Moose Lake
Cooper, Jack M. ..... St. Paul
† Countryman, Roger S. ..... Saratoga, CA
‡ Craig, David M. ..... St. Paul
#‡ Cram, Barclay M. ..... St. Paul
‡ Cramer, Glen G. ..... New Brighton
Crowley, James H. ..... St. Paul
‡ Crudo, Vincent D. ..... St. Paul
‡ Crum, Arthur Z. ..... St. Paul
Crutchfield, Charles E. ..... St. Paul
Crutchfield, Susan E. ..... St. Paul
Culligan, David E. ..... St. Paul
‡ Culligan, John A. ..... St. Paul
‡ Culver, Lucian G. ..... St. Paul
‡ Cumming, Edward D. ..... St. Paul
‡ Daly, Alfred E. ..... St. Paul
‡ Damberg, Sheldon W. ..... St. Paul
‡ Davis, Edward V. ..... St. Paul
Davis, Eunice A. ..... St. Paul
* Decker, Charles H. ..... St. Paul
‡ Derauf, Donald E. ..... St. Paul
‡ Derechin, William ..... St. Paul
‡ Deters, Donald C. ..... St. Paul
Dickinson, Paul B. ..... St. Paul
Dieperink, Willem ..... St. Paul
†‡ Dittrich, Raymond J. ..... St. Paul
Dolmage, George H. ..... St. Paul
‡ Dooley, Robert T. ..... St. Paul
Duerr, Eleanor E. ..... St. Paul
‡ Dunn, James P. ..... St. Paul
Dunn, Robert C. ..... St. Paul
‡ Durkin, John L. ..... St. Paul
‡ Duthoy, Everette J. ..... St. Paul
‡ Duvall, Arndt J., III ..... St. Paul
Drydal, Paul J. ..... St. Paul
† Earl, George A. ..... St. Paul
‡ Earl, John R. ..... St. Paul
Edwards, J. Willard ..... St. Paul
‡ Edwards, Jesse E. ..... St. Paul
Edwards, Laura E. ..... St. Paul
Edwards, Lloyd G. ..... St. Paul
† Edwards, Richard B. ..... St. Paul
Edwards, Thomas J. ..... St. Paul
Edwardson, Phillip L. ..... St. Paul
‡ Eelkema, Herman H. ..... St. Paul
Eginton, Charles T. ..... Fargo, ND
‡ Eilers, Vincent E. ..... St. Paul
Elliott, William G. ..... St. Paul
Ellis, Ronald W. ..... St. Paul
Elumba, Teodoro V. ..... St. Paul
Emerson, Edward C. ..... St. Paul
‡ Emmons, Robert W. ..... St. Paul
Endress, Edward K. ..... St. Paul
‡ England, Rodney W. ..... St. Paul
‡ Enroth, Oscar E. ..... St. Paul
Erickson, Donald L. ..... St. Paul
Erlanson, A. Cornell ..... St. Paul
‡ Erling, Carl B. ..... St. Paul
‡ Ersfeld, Murray P. ..... St. Paul
*‡ Farkas, John V. ..... St. Paul
Farr, John D. ..... St. Paul
‡ Fee, John G. ..... St. Paul
‡ Felder, Davitt A. ..... St. Paul
‡ Felion, Arthur J. ..... St. Paul
‡ Ferguson, John N. ..... St. Paul
† Fesler, Harold H. ..... West St. Paul
‡ Fink, Daniel L. ..... St. Paul
‡ Fischer, Robert F. ..... St. Paul
Flanagan, Kathleen R. ..... St. Paul
‡ Flannery, Hubert F. ..... St. Paul
Flom, Reynold P. ..... St. Paul
‡ Flom, Robert S. ..... St. Paul
‡ Flynn, Louis L., Jr. ..... St. Paul

Ramsey County Medical Society *(Continued)*

‡ Flynn, Robert A. ..... St. Paul
‡ Fogelberg, Emil J. ..... St. Paul
‡ Foreman, Richard T. ..... St. Paul
Forsythe, James R. ..... St. Paul
‡ Fox, LeRoy J. ..... St. Paul
‡ Freeman, Charles D. ..... St. Paul
Fritz, Wallace L. ..... St. Paul
‡ Froats, Charles W. ..... St. Paul
Frost, John W. ..... St. Paul
‡ Frye, Charles W. ..... St. Paul
‡ Fuller, Benjamin F. ..... White Bear Lake
Funke, Joyce L. ..... St. Paul
‡ Gaertner, Frank M. J., Jr. ..... St. Paul
‡ Gaertner, John R. ..... St. Paul
‡ Galligan, John J. ..... St. Paul
‡ Gardner, Walter P. ..... St. Paul
Garrow, Douglas M. ..... St. Paul
Gaute, Svend T. ..... St. Paul
‡ Gedgaudas, Eugene ..... St. Paul
†‡ Gehlen, Joseph N. ..... St. Paul
‡ Geist, Robert W. ..... St. Paul
‡ Gendron, Joseph L. ..... Minneapolis
Gibbs, Edward C. ..... St. Paul
‡ Gilchrist, Milton R. ..... St. Paul
‡ Gillespie, Delmar R. ..... St. Paul
‡ Gilsdorf, Donald A. ..... St. Paul
‡ Glenny, William R. ..... St. Paul
Gold, Ernest M. ..... St. Paul
‡ Goldberg, Robert J. ..... St. Paul
‡ Goldsmith, Joseph W. ..... St. Paul
Goodman, Ernest ..... St. Paul
‡ Goott, Bernard ..... St. Paul
‡ Govrik, Kalman ..... St. Paul
‡ Greene, Jerry G. ..... St. Paul
‡ Gretsch, Gerald A. ..... St. Paul
Gridley, John W. ..... Minneapolis
‡ Griffin, Patrick J. ..... St. Paul
‡ Griffin, Thomas M. ..... St. Paul
‡ Gruninger, Robert P. ..... St. Paul
‡ Gudio, Felix A., Jr. ..... St. Paul
‡ Gumnit, Robert J. ..... St. Paul
‡ Guthrie, J. Cameron ..... St. Paul
‡ Haight, James W. ..... Ft. Snelling
Hakanson, Erick Y. ..... St. Paul
‡ Hall, Barnard ..... St. Paul
‡ Hammes, Ernest M., Jr. ..... St. Paul
‡ Hannon, Donald W. ..... St. Paul
‡ Hanton, Edward M. ..... St. Paul
Harmon, Gaius E. ..... St. Paul
‡ Harris, John E. ..... Minneapolis
‡ Harris, Max E. ..... St. Paul
‡ Hartfiel, William F. ..... St. Paul
Hartig, Marjorie ..... St. Paul
Haus, Erhard ..... St. Paul
‡ Hauser, Charles W. ..... St. Paul
†‡ Hauser, Victor P. ..... St. Paul
‡ Hawkinson, Harlan W. ..... St. Paul
‡ Hayes, Albert F. ..... St. Paul
†‡ Heck, William W. ..... St. Paul
‡ Hedenstrom, Charles W. ..... St. Paul
† Hedenstrom, Frank G. ..... St. Paul
‡ Hedenstrom, Richard H. ..... St. Paul
† Hedlund, Charles J. ..... St. Paul
‡ Henderson, Terrance ..... White Bear Lake
† Hengstler, William H. ..... St. Paul
‡ Henke, Wilbert J. ..... St. Paul
‡ Henry, James S. ..... St. Paul
Herman, Samuel M. ..... St. Paul
‡ Herrick, Donald W. ..... St. Paul
† Hetzler, John A. ..... White Bear Lake
‡ Hilger, Jerome A. ..... St. Paul
‡ Hilger, Laurence D. ..... St. Paul
‡ Hilgers, Robert D. ..... Minneapolis
‡ Hilker, Marcus D. ..... St. Paul
Hill, Charlotte W. ..... St. Paul
Hinckley, Robert G. ..... White Bear Lake
† Hiniker, Louis P. ..... St. Paul
Hippchen, Ray C. ..... St. Paul
‡ Ho, Shu Kang ..... St. Paul
‡ Hodgson, Corrin H. ..... St. Paul
Hodgson, Jane E. ..... St. Paul
‡ Hohmann, Albert ..... St. Paul
*† Holcomb, O. William ..... St. Paul
Hollinshead, William H. ..... St. Paul
†‡ Holt, John E. ..... St. Paul
Hopkins, G. Wendell ..... Minneapolis
‡ Hottinger, George C. ..... St. Paul
Houle, Rollin J. ..... New Brighton
Houlton, William H. ..... St. Paul
Howe, Newell W. ..... West St. Paul
Hunt, Vincent R. ..... Minneapolis
‡ Hunter, Samuel W. ..... St. Paul
‡ Hurwitz, Milton M. ..... St. Paul
‡ Huseby, Thomas L. ..... St. Paul
‡ Husebye, Kjeld O. ..... St. Paul
Ireland, Gerald W. ..... St. Paul
‡ Jackson, William C. ..... St. Paul
‡ James, Ellery M. ..... St. Paul
‡ James, John W. ..... St. Paul
‡ Janecek, James, ... New Brighton
‡ Janssen, Martin E. ..... St. Paul
Jarvis, Charles W. ..... St. Paul
‡ Jastram, Rupert M. ..... St. Paul
Johnson, Carl E. ..... St. Paul
Johnson, Carolyn A. ..... St. Paul
† Johnson, Daniel T. ..... St. Paul
‡ Johnson, Herbert W. ..... St. Paul
Johnson, Lyle O. ..... A.P.O. New York, NY
‡ Johnson, Richard J. ..... St. Paul
Johnson, Robert H. ..... St. Paul
‡ Johnson, Rodger L. ..... St. Paul
‡ Johnson, Thomas E. ..... St. Paul
Jorgensen, Donald R. ..... St. Paul
Joseph, Arnold H. ..... St. Paul
‡ Kantar, Yale C. ..... St. Paul
Kaplan, David H. ..... Edina
‡ Karon, Everett H. ..... St. Paul
‡ Karon, Irvine M. ..... St. Paul
‡ Kasper, Eugene M. ..... St. Paul
Katz, Louis J. ..... Long Beach, CA
*‡ Kelly, Albert C. ..... St. Paul
‡ Kelly, Edward H. ..... St. Paul
Kelly, Helen M. ..... Cottage Grove
‡ Kelly, Joseph R. ..... St. Paul
‡ Kelsey, Chauncey M. ..... St. Paul
†‡ Kenefick, Emmett V. ..... St. Paul
‡ Kenyon, Thomas J. ..... St. Paul
† Kesting, Herman ..... St. Paul
Kleinsasser, Warren L. ..... Farmington
‡ Knowles, Roy C. ..... St. Paul
Knutson, Robert C. ..... West St. Paul
Kodres, Nina ..... St. Paul
Koelz, Thomas A. ..... St. Paul
‡ Kosiak, Michael ..... St. Paul
Koza, Donald W. ..... St. Paul
Kraatz, Robert W. ..... Phenix City, AL
‡ Kramer, James D. ..... St. Paul
‡ Krezowski, Thomas K. ..... St. Paul

Continued on Next Page

Ramsey County Medical Society *(Continued)*

‡ Kugler, Alex A. ..... St. Paul
‡ Kuske, Albert W. ..... St. Paul
‡ Kusske, Bradley W. ..... St. Paul
‡ Kusske, Douglas R. ..... St. Paul
‡ Kvam, Lowell ..... St. Paul
Lade, Roswith I. ..... St. Paul
‡ LaFave, James W. ..... St. Paul
‡ Lampert, Ronald M. ..... St. Paul
‡ Lane, Miles I. ..... White Bear Lake
‡ Lannin, Bernard G. ..... St. Paul
‡ Lannin, Donald R. ..... St. Paul
Larkin, John E. ..... St. Paul
Larson, Eva Jane Ostergren ..... St. Paul
‡ Larson, Jerrold V. ..... St. Paul
† Laszewski, Franz Von Zelberschwecht ..... St. Paul
‡ Lawler, Kevin M. ..... St. Paul
Layman, Thomas E. ..... St. Paul
Leahy, Dennis M. ..... St. Paul
† Leach, Clifford G. ..... St. Paul
‡ Lees, Jack R. ..... St. Paul
Lehman, Donald S. ..... St. Paul
‡ Leick, Richard M. ..... St. Paul
† Leitch, Archibald ..... South St. Paul
Leonard, Stanley ..... St. Paul
‡ Lerdahl, Kenneth ..... St. Paul
‡ Lerner, Irving J. ..... St. Paul
Lessard, Richard J. ..... St. Paul
Leven, N. Logan ..... St. Paul
‡ Leverenz, Carleton W. ..... St. Paul
‡ Levitan, Leonard H. ..... St. Paul
Levitt, George X. ..... St. Paul
Lewis, Joyce S., Jr. ..... Minneapolis
*† Lick, Charles L. ..... St. Paul
‡ Lick, William J. ..... St. Paul
‡ Lien, Richard J. ..... St. Paul
† Lightbourn, Edgar L. ..... Hastings
‡ Lilleberg, Norbert J. ..... St. Paul
Lillie, Andrew R. ..... St. Paul
‡ Lindell, Robert E. ..... St. Paul
‡ Lindquist, Max F. ..... South St. Paul
Lippman, Hyman S. ..... St. Paul
Litkewitsch, Helene ..... St. Paul
† Lobell, Michael ..... St. Paul
‡ Loken, Selmer M. ..... St. Paul
Lowe, Alexander D. ..... South St. Paul
† Lowe, Thomas A. ..... South St. Paul
‡ Lufkin, Murray W. ..... St. Paul
†‡ Lundholm, Arthur M. ..... Princeton
‡ Lunzer, Richard G. ..... St. Paul
‡ Lynch, Francis W. ..... St. Paul
‡ Lynch, Raymond P. ..... St. Paul
‡ Lynch, Richard P. ..... St. Paul
McBride, John W. ..... St. Paul
‡ McCafferty, Charles W. ..... St. Paul
‡ McCain, Donovan L. ..... St. Paul
‡ McCarthy, Charles J. ..... St. Paul
McClellan, Robert J. ..... St. Paul
McCloud, C. Naumann ..... St. Paul
‡ McEllistrem, Edward J. ..... St. Paul
‡ McEllistrem, Gerald D. ..... St. Paul
‡ McEwan, Alexander ..... St. Paul
‡ McGroarty, Brian J. ..... St. Paul
‡ McHutchinson, Samuel K. ..... St. Paul
McKenzie, Eva E. ..... St. Paul
‡ McNeill, John A. ..... St. Paul
MacCornack, Robert L., Jr. ..... South St. Paul
Mackoff, Sam M. ..... Phoenix, AZ
Madland, Robert S. ..... St. Paul
Magary, Victor J., Jr. ..... So. Ft. Mitchell, KY
Malerich, J. Anthony ..... Cottage Grove
‡ Manlove, Charles H. ..... St. Paul
‡ Marta, John B. ..... St. Paul
‡ Martin, Dwight L. ..... St. Paul
Mateo, Guillermo ..... St. Paul
Matthews, James H. ..... Minneapolis
Matus, Richard N. ..... St. Paul
‡ Mazzitello, William F. ..... St. Paul
‡ Mears, Burtis J. ..... St. Paul
‡ Medelman, John P. ..... St. Paul
‡ Melancon, Joseph F. ..... St. Paul
‡ Merrick, Robert L. ..... St. Paul
Michienzi, Leonard J. ..... St. Paul
‡ Miller, Albert G. ..... St. Paul
Miller, Winston R. ..... St. Paul
Miller, Zondal R. ..... St. Paul
‡ Milnar, Frank J. ..... St. Paul
Milroy, Thomas W. ..... Minneapolis
‡ Mishek, Charles J. ..... St. Paul
‡ Mitchell, George S. ..... St. Paul
† Molander, Herbert A. ..... St. Paul
‡ Moller, Jurgen J. ..... West St. Paul
‡ Monahan, Robert H. ..... St. Paul
‡ Mooney, Robert D. ..... St. Paul
Moren, J. Adelaide ..... St. Paul
‡ Mowlem, Albert ..... St. Paul
Mulford, Beatrice ..... St. Paul
‡ Muller, A. Eugene ..... North St. Paul
Mundahl, Harold R. ..... St. Paul
Murphy, Jack T. ..... St. Paul
Nauth, Bernard S. ..... Minneapolis
‡ Neher, Frederick J. ..... St. Paul
Neira, Edward H. ..... St. Paul
† Nelson, David J. ..... St. Paul
‡ Nelson, Delbert R. ..... St. Paul
‡ Nelson, Loren E. ..... St. Paul
‡ Nelson, Louis A. ..... St. Paul
Nelson, Robert P. ..... St. Paul
‡ Nelson, Ronald J. ..... St. Paul
Nesvacil, Leon ..... St. Paul
‡ Nichols, Thomas O. ..... St. Paul
†‡ Nimlos, Kenneth O. ..... St. Paul
† Nimlos, Lenore O. ..... St. Paul
‡ Norman, David D. ..... St. Paul
Norquist, Joseph L. ..... St. Paul
Nuebel, Charles J. ..... Long Beach, CA
† Nye, Lillian L. ..... St. Paul
O'Brien, Gerald R. ..... Minneapolis
‡ O'Brien, John C. ..... St. Paul
‡ O'Kane, Thomas W. ..... St. Paul
‡ O'Malley, Valentine ..... St. Paul
O'Neill, Nial C. ..... St. Paul
† O'Reilley, Bernard E. ..... Sun City, AZ
Ockuly, Orville E. ..... St. Paul
† Ogden, Warner ..... River Falls, WI
† Ohage, Justus ..... St. Paul
‡ Olsen, Ralph L. ..... St. Paul
Olson, Barbara F. ..... St. Paul
‡ Osekowsky, Henry J. ..... St. Paul
*†‡ Ostergren, Edward W. ..... St. Paul
‡ Ouellette, Alfred ..... St. Paul
‡ Owens, Frederick M., Jr. ..... St. Paul
‡ Palm, Neil M. ..... St. Paul
‡ Paulson, Elmer C. ..... St. Paul
‡ Paulson, Wallace J. ..... St. Paul
Peake, Janna Zoe ..... St. Paul
† Pearson, Fritz R. ..... St. Paul
‡ Pearson, Malcolm M. ..... St. Paul
† Pedersen, Arthur H. ..... St. Paul
‡ Pelletier, Rene W. ..... St. Paul

Ramsey County Medical Society *(Continued)*

‡ Perry, John F., Jr. ..... St. Paul
‡ Peterson, Donald H. ..... St. Paul
‡ Peterson, Edward A. ..... St. Paul
‡ Peterson, Harold O. ..... Minneapolis
† Peterson, Joel L. E. ..... St. Paul
Peterson, Roy L. ..... White Bear Lake
Phillips, Leonard ..... St. Paul
‡ Pilney, Frank T. ..... St. Paul
Plotke, Harry L. ..... St. Paul
Polski, Paul G. ..... South St. Paul
Poole, James R. ..... Wheaton
‡ Post, Edmund A. ..... St. Paul
‡ Powers, Robert L. ..... St. Paul
Prentice, Walter B. ..... Minneapolis
‡ Proud, Harry S. ..... St. Paul
Quattlebaum, Frank W. ..... St. Paul
‡ Raaen, Olaf J. ..... St. Paul
Rabcevich, Anatole ..... St. Paul
‡ Ralph, James R. ..... St. Paul
‡ Ramlow, Ralph M. ..... West St. Paul
† Ramsey, Walter R. ..... St. Paul
‡ Raths, Otto N., Jr. ..... St. Paul
‡ Ravits, Harold G. ..... St. Paul
‡ Rea, Charles E. ..... St. Paul
Redleaf, Paul D. ..... St. Paul
Reid, James W. ..... South St. Paul
‡ Reif, Robert W. ..... St. Paul
Rice, Frank B. ..... St. Paul
‡ Richardson, Edward J., Jr. ..... St. Paul
‡ Rick, Paul F. W. ..... St. Paul
‡ Rinkey, Eugene ..... St. Paul
† Ripple, Rudolph J. ..... St. Paul
†‡ Ritt, Albert E. ..... St. Paul
‡ Roach, Charles A. ..... St. Paul
‡ Roach, Donald E. ..... St. Paul
‡ Rolig, David H. ..... West St. Paul
Rollie, Orris O. ..... St. Paul
Romero, Jose B. ..... St. Paul
†‡ Rosenthal, Robert ..... St. Paul
Rossing, Robert G. ..... Brooks AFB, TX
‡ Roth, George C. ..... St. Paul
‡ Rowe, Clarence J., Jr. ..... St. Paul
‡ Roy, Philemon C. ..... St. Paul
† Ruhberg, George N. ..... Santa Barbara, CA
‡ Rukavina, John G. ..... St. Paul
‡ Rushay, Arthur J. ..... White Bear Lake
‡ Rusterholz, Alan P. ..... St. Paul
†‡ Ryan, John J. ..... St. Paul
‡ Ryan, Joseph M. ..... St. Paul
‡ Sand, Richard E. ..... St. Paul
‡ Sandkamp, Virgil A. ..... South St. Paul
‡ Sargent, John H. ..... St. Paul
‡ Savett, Laurence A. ..... St. Paul
Saxena, Krishna M. ..... St. Paul
‡ Schaffhausen, George E. ..... St. Paul
‡ Scherek, Jerome J. ..... St. Paul
‡ Schloff, Ivan ..... St. Paul
‡ Schloff, Leonard D. ..... St. Paul
Schmidtke, Reinhardt L. ..... Minneapolis
*† Schoch, Robert B. J. ..... St. Paul
‡ Schochet, H. Laurence ..... St. Paul
† Schons, Edward ..... Minnetonka Beach
‡ Schossow, George W. ..... White Bear Lake
‡ Schrader, Wayne H. ..... St. Paul
‡ Schroeckenstein, Hugo F. ..... St. Paul
‡ Schultz, Paul E. ..... St. Paul
Schwartzkopff, Othild ..... St. Paul
‡ Scott, Eugene E. ..... St. Paul
Sekhon, Mohan S. ..... St. Paul
‡ Sells, Richard J. ..... St. Paul
‡ Sethre, Arthur ..... St. Paul
†‡ Setzer, Hobert J. ..... St. Paul
† Shannon, William R. ..... Faribault
Shear, Howard H. ..... West St. Paul
‡ Shelander, Marcus I. ..... St. Paul
Siegel, Clarence ..... St. Paul
‡ Siegel, Leighton G. ..... St. Paul
Simmonds, Harry N. L. ..... St. Paul
‡ Simons, Leander T. ..... St. Paul
‡ Singer, Benjamin J. ..... St. Paul
‡ Skinner, Abbott ..... St. Paul
† Skinner, Harvey O. ..... St. Paul
‡ Smiley, Donald P. ..... St. Paul
‡ Smisek, Elmer A. ..... St. Paul
‡ Smith, H. Nippert ..... St. Paul
‡ Smith, Vernon D. E. ..... St. Paul
‡ Smith, William T. ..... St. Paul
† Snyder, George W. ..... St. Paul
†‡ Sohlberg, Olof I. ..... St. Paul
‡ Sommerdorf, Vernon L. ..... St. Paul
Sorem, Milton B. ..... St. Paul
Soucheray, Philip H. ..... St. Paul
†‡ Souster, Benjamin B. ..... St. Paul
‡ Sowada, Ernest J. ..... St. Paul
‡ Sperl, Michael P., Jr. ..... St. Paul
‡ Sprafka, Gregory A. ..... St. Paul
‡ Sprafka, Joseph L. ..... St. Paul
‡ Spraitz, Anton F., Jr. ..... St. Paul
‡ Stafne, John G. ..... St. Paul
Stein, Robert L. ..... Northridge, CA
‡ Steinberg, Charles L. ..... St. Paul
‡ Sterner, Donald C. ..... St. Paul
‡ Sterner, Ernest R. ..... St. Paul
‡ Sterner, John J. ..... St. Paul
‡ Stolee, Thomas A. ..... St. Paul
Straus, Maurice L. ..... St. Paul
‡ Strem, Edward L. ..... St. Paul
‡ Sturley, Rodney F. ..... St. Paul
‡ Sullivan, W. Albert, Jr. ..... St. Paul
‡ Swanson, Lawrence J. ..... West St. Paul
‡ Swanson, Ralph H. ..... West St. Paul
Swendson, James J. ..... St. Paul
‡ Swenson, Donald B. ..... St. Paul
‡ Taddeini, Luigi ..... St. Paul
‡ Tanasichuk, Murray A. ..... St. Paul
‡ Tani, George ..... St. Paul
Tate, Wayne E. ..... South St. Paul
‡ Teeter, Richard R. ..... St. Paul
‡ Teisberg, John E. ..... St. Paul
‡ Thalhuber, Wayne H. ..... St. Paul
‡ Thompson, Wayne W. ..... St. Paul
‡ Tiffany, Francis B. ..... St. Paul
‡ Tifft, Cyril R. ..... St. Paul
‡ Tongen, Lyle A. ..... St. Paul
‡ Travis, James S. ..... St. Paul
Tregilgas, Richard B. ..... St. Paul
‡ Trotmar, Neil M. ..... St. Paul
‡ Troup, Elliott ..... St. Paul
Trow, William H. ..... St. Paul
Tveten, Omar A. ..... St. Paul
‡ Ubel, Frank A. ..... St. Paul
Vaccarella, R. James ..... St. Paul
Vail, David J. ..... St. Paul
Valentini, Eugene J. ..... St. Paul
Van Bergen, Frederick H. ..... Minneapolis
‡ Van De Riet, Lowell W. ..... St. Paul
Varco, Richard L. ..... St. Paul
‡ Vaughn, C. Gordon ..... St. Paul

Continued on Next Page

Ramsey County Medical Society *(Continued)*

Veinbergs, Arnold ..... St. Paul
Veirs, Dean M. ..... Hastings
† Venables, Alexander E. ..... Marysville, WV
‡ Venters, Homer D., Jr. ..... St. Paul
‡ Votel, Thomas W. ..... St. Paul
‡ Waas, Charles W. ..... St. Paul
† Walker, Arthur E. ..... St. Paul
‡ Wall, James O. ..... St. Paul
‡ Walsh, Edward F. ..... St. Paul
‡ Walter, Clarence W. ..... St. Paul
‡ Warner, Clyde M. ..... St. Paul
‡ Warren, Cecil A. ..... St. Paul
Waters, Alvin W. ..... St. Paul
‡ Watson, P. Theodore ..... St. Paul
‡ Watson, William H. A. ..... St. Paul
‡ Watson, William J. ..... Newport
Watz, Clarence E. ..... St. Paul
‡ Webb, Alex G. ..... St. Paul
‡ Webber, Fred L. ..... St. Paul
‡ Wedes, Deno J. ..... St. Paul
Wegleitner, Mark J. ..... Fort Sill, OK
† Weier, Thomas E. ..... St. Paul
Weigant, Charles E. ..... Fort Snelling
‡ Weis, Benjamin A. ..... St. Paul
†‡ Weisberg, Maurice ..... St. Paul
‡ Wenzel, Gilbert P. ..... St. Paul
† Westermeyer, Joseph J. ..... St. Paul
‡ Westover, Darrell E. ..... St. Paul
Wetteland, Thomas F. ..... West St. Paul
‡ Wetzel, Earl V. ..... St. Paul
Whiting, F. Douglas ..... St. Paul
‡ Wiencke, William M. ..... St. Paul
‡ Wier, G. Thomas ..... St. Paul
† Williams, Harry J., III ..... St. Paul
‡ Williams, George E. ..... St. Paul
‡ Williams, Hugh J. ..... St. Paul
‡ Williams, John A. ..... St. Paul
Williams, Richard A. ..... Cottage Grove
‡ Wilson, Fred B. ..... St. Paul
‡ Winter, Robert B. ..... St. Paul
Wolfson, Justin J. ..... St. Paul
Wolkoff, Hyman J. ..... St. Paul
‡ Woodburn, Robert L. ..... St. Paul
‡ Woolfrey, Bertram F. ..... St. Paul
Ya, Po Myat ..... St. Paul
YaDeau, Richard E. ..... St. Paul
Youngren, Everett R. ..... St. Paul
‡ Zachman, Leo L. ..... St. Paul
‡ Zagaria, James F. ..... St. Paul
‡ Zarling, Max E. ..... St. Paul

RANGE MEDICAL SOCIETY

Koochiching, Itasca and the Northern Portion of
St. Louis County
Regular meetings, fourth Tuesday of the Month
Annual meeting, January
Number of members 111

PRESIDENT
Flynn, Bernard F. ..... Hibbing
SECRETARY
Alexander, Paul J. ..... Hibbing
CORRESPONDING SECRETARY
Evans, Mrs. Virginia ..... Hibbing
Ahola, Kenneth E. ..... Hibbing
Alexander, Paul J. ..... Hibbing
Anderson, Russell H. ..... Virginia
Antonelli, Jordan J. ..... Hibbing
Antonow, Arthur M. ..... Virginia
Arko, Frank R. ..... Hibbing
Avren, Barbara L. ..... Virginia
Baich, Velemir M. ..... Coleraine
Balderson, Robert P. ..... Grand Rapids
Baraga, Anthony R. ..... Hibbing
Barnes, Richard E. ..... Aurora
Bartholdt, H. Peter ..... Cook
† Benell, Otto E. ..... Britt
Bolz, J. Arnold ..... Grand Rapids
Bonner, John L. ..... Grand Rapids
† Brende, Joel O. ..... Topeka, KS
Braun, Ohrmundt C. ..... Grand Rapids
Campos, Armador ..... Aurora
*† Cantwell, William F. ..... International Falls
Chermak, Francis G. ..... Phoenix, AZ
‡ Ciriacy, Edward W. ..... Ely
Coe, Robert O. ..... Virginia
Cope, Hershel B. ..... Virginia
Coy, Douglas J. ..... Grand Rapids
Crow, George M. ..... International Falls
DeMarais, Lloyd C. ..... Hibbing
Decker, Charles W. ..... Hibbing
Dobler, Manfred G. ..... Ely
Drucker, Franklin G. ..... Bigfork
Eisenman, Walter ..... Hibbing
‡ Engelstad, Wendell P. ..... Virginia
Erickson, Vernon D. ..... Grand Rapids
Evensta, John B. ..... Grand Rapids
Ewens, George B. ..... Virginia
Flynn, Bernard F. ..... Hibbing
French, Bayard T. ..... Hibbing
Friedlieb, Oskar P. ..... Virginia
Gerend, Thomas J. ..... Virgina
Glomstad, Gary B. ..... Grand Rapids
Goodall, David C. ..... Deer River
Grahek, Jack P. ..... Ely
Grinley, Andrew V. ..... Grand Rapids
Halper, Bernard ..... Hibbing
Halverson, Kermit J. ..... Parkville
Hanover, Ralph D. ..... International Falls
Hansen, Robert E. ..... Hibbing
† Heiam, William C. ..... Cook
Helwig, Karl L. ..... Virginia
Holm, Owen W. ..... Hibbing
Ibrahim, George W. ..... Virginia
Iverson, Paul C. ..... Grand Rapids
† Jacobson, Clarence ..... Chisholm
Johnson, Calvin J. ..... Grand Rapids
Johnsrud, Luverne ..... Hibbing
Johnston, H. Wayne ..... Virginia
Karges, Laurel E. ..... Grand Rapids
Karish, Louis J. ..... Grand Rapids
‡ Kelly, Robert T. ..... Grand Rapids
Kiesler, Frank ..... Grand Rapids
† Kotchevar, Frank R. ..... Sun City, CA

Range Medical Society *(Continued)*

Kruger, E. Larry ..... Nashwauk
Law, Harrison E. ..... Virginia
Leach, Thomas C. ..... Babbitt
Lee, William C. ..... Hibbing
McClelland, John G. ..... Virginia
McKenna, John J. ..... Virginia
McKenna, Maurice J. ..... Grand Rapids
McLeod, John A. ..... Chisholm
Martinson, Raymond M. ..... Virginia
Mast, Fredric L. ..... Chisholm
Miettunen, John B. ..... Hibbing
Miks, George M. ..... Aurora
Miller, Harry G. ..... Virginia
Mock, Charles J. ..... Virginia
Moyer, Richard R. ..... Hibbing
Mueller, Donald R. ..... Grand Rapids
‡ Muller, John J. ..... Hibbing
Murray, Robert A. ..... Hibbing
Neff, Walter S. ..... Britt
Nelimark, Donald R. ..... Virginia
Nelson, Bernette G. ..... Ely
Nixon, Rodney T. H. ..... Grand Rapids
‡ Nollet, Donald J. ..... Hibbing
Olson, Richard T. ..... Virginia
Owens, Ben P. ..... Hibbing
Parker, Wilbert H. ..... Chisholm
Paciotti, Vincent J. ..... Hibbing
Payne, Richard E. ..... Virginia
Person, Duane F. ..... Virginia
Peterson, Edward N. ..... Virginia
Pietan, Jerald H. ..... Chisholm
Prlina, Isaac M. ..... Virginia
Reed, Paul ..... Virginia
Reynolds, Dermot F. ..... Hibbing
Richter, David J. ..... Virginia
Roth, Albert H. ..... Deer River
† Rowles, Everett K. ..... Laguna Hills, CA
†‡ Salter, Reginald A. ..... Virginia
‡ Schirber, Martin J. ..... Grand Rapids
‡ Schweiger, Theodore R. ..... Hibbing
Sher, David A. ..... Virginia
Siegel, John S. ..... Virginia
*†‡ Sinamark, Andrew ..... Hibbing
† Sisler, Clifford E. ..... Grand Rapids
† Snyker, Omer E. ..... Ely
Stolen, Keith H. ..... Grand Rapids
Strouth, Jonas C. ..... Virginia
Summar, M. Thomas ..... Virginia
Swenson, Floyd J. ..... Grand Rapids
Talsness, Jon M. ..... International Falls
Tietz, Charles A. ..... Virginia
‡ Walker, Stuart B. ..... Aurora
‡ Walter, Frederick H. ..... International Falls
Weir, Mathew J. ..... Virginia
‡ Werner, Donald L. ..... Hoyt Lakes
Wheeler, Gilbert S. ..... Virginia
‡ Woodruff, Whitney ..... Virginia

RED RIVER VALLEY MEDICAL SOCIETY

Kittson, Mahnomen, Marshall, Norman, Pennington, Polk, Red Lake and Roseau Counties
Regular meetings, quarterly
Annual meeting, December
Number of members 58

PRESIDENT

Stadem, Clifford ..... Crookston

SECRETARY

Dagg, Earl ..... Thief River Falls
Baab, Robert O. ..... Crookston
Behr, Orlo K. ..... Crookston
‡ Berg, Arnold M. ..... Thief River Falls
† Bratrud, Edward ..... Alexandria
Bray, Jerome L. ..... Thief River Falls
Brown, Glenn W. ..... Halstad
Cameron, John H. ..... Clovis, NM
Carter, Robert G. ..... Thief River Falls
Clapp, Hubert D. ..... Crookston
Dagg, Earl ..... Thief River Falls
Davidson, Duane J. ..... Thief River Falls
Delmore, John L. ..... Roseau
Dillenburg, Cyril ..... Crookston
† Flancher, Leon H. ..... Detroit Lakes
† Foderick, Peter P. ..... Ada
Herber, Leo ..... Thief River Falls
Hirsh, Stanton ..... Crookston
Holmstrom, Carle H. ..... Warren
Jensen, John A. ..... Crookston
Kinkade, Byron R. ..... Ada
‡ Klefstad, Lloyd H. ..... Greenbush
† Kostick, William R. ..... Fertile
Larter, Roland R. ..... Hallock
† Loken, Theodore ..... Ada
† Lynde, Orrin G. ..... Los Gatos, CA
Martin, George B. ..... Thief River Falls
Melashenko, Kenneth W. ..... Karlstad
Mercil, C. B. ..... Mahnomen
Mercil, William ..... Crookston
Mersy, David J. ..... Red Lake Falls
Montaniel, Necito L. ..... Crookston
† Nelson, Henry E. ..... Crookston
† Oppegaard, C. L. ..... Scottsdale, AZ
Parra, Samuel ..... Crookston
Pinsonneault, W. A. ..... Roseau
Pollman, Stanley E. ..... Naha, Okinawa
Pumala, Erven E. ..... Warren
Reff, Alan R. ..... Crookston
† Roholt, Christian L. ..... McIntosh
Rubin, Jacob S. ..... Crookston
† Sather, R. Alan ..... Oklahoma City, OK
Sather, Edgar L. ..... Fosston
Sather, George A. ..... Fosston
‡ Sather, Richard N. ..... Fosston
Sather, Russell O. ..... Crookston
Scheuneman, Allen F. ..... Thief River Falls
Schnabel, Norma B. ..... Crookston
Schnabel, Robert F. ..... Crookston
Skogerboe, Rudolph B. ..... E. Grand Forks
Stadem, Clifford ..... Crookston
Stewart, Donald E. ..... Crookston
Taylor, Ross M. ..... Thief River Falls
Thorsgard, Ernest O. ..... Thief River Falls
Uhley, Charles G. ..... Crookston
Van Rooy, George T. ..... Thief River Falls
Wendt, Paul ..... Thief River Falls
Wikoff, Howard M. ..... Crookston

RENVILLE-REDWOOD COUNTY MEDICAL SOCIETY

Renville and Redwood Counties
Regular meetings, March, June, September and December
Annual meeting, December
Number of members 12

PRESIDENT
Nelson, Glenn E. ..... Redwood Falls
SECRETARY
Flinn, James B. ..... Redwood Falls
‡ Anderson, Chester A. ..... Hector
† Brand, William A. ..... Redwood Falls
†‡ Ceplecha, Stanley F. ..... Redwood Falls
Cosgriff, James A., Jr. ..... Olivia
†‡ Eilers, William B. ..... Redwood Falls
† Fawcett, Arthur M. ..... Renville
‡ Flinn, James B. ..... Redwood Falls
‡ Furr, Leo O. ..... Bird Island
‡ Kaminski, Gregory W. ..... Redwood Falls
Lenz, Joseph R. ..... Morton
‡ Nelson, Glenn E. ..... Redwood Falls
‡ Strauchler, John ..... Belview

RICE COUNTY MEDICAL SOCIETY

Rice County
Regular meetings, third Tuesday of
January, April, September and November
Annual meeting in November
Number of members 31

PRESIDENT
Street, Bernard ..... Northfield
SECRETARY
Clarke, Dean T. ..... Faribault
Bauer, Paul G. ..... Faribault
‡ Beaton, J. Gordon ..... Northfield
‡ Bruhl, Heinz H. ..... Faribault
Buesgens, Ralph H. ..... Waterville
Clarke, Dean ..... Faribault
† Engberg, Edward J. ..... Faribault
Faust, John H. ..... Northfield
‡ Francis, David W. ..... Morristown
Good, Roy H. ..... Northfield
‡ Graham, Asa B. ..... Faribault
Gutzmann, Bruce F. ..... Faribault
‡ Haas, Jack F. ..... Northfield
‡ Halvorson, David C. ..... Northfield
† Kennedy, George L. ..... Faribault
† Kolars, James J. ..... Faribault
Meyer, Frederick C. ..... Kenyon
† Meyer, Paul F. ..... Faribault
Meyer, Richard H. ..... Faribault
Meyer, Robert P. ..... Faribault
Nickerson, John R. ..... Faribault
‡ Orr, Burton A. ..... Faribault
† Rumpf, Carl W. ..... Faribault
Rysgaard, George N. ..... Northfield
Smith, Thorsten ..... Theills, NY
‡ Speckhals, Robert C. ..... Faribault
‡ Street, Bernard ..... Northfield
Studer, Donald J. ..... Faribault
† Traeger, Carl A. ..... Faribault
‡ Tuma, Ben ..... Faribault
‡ Watts, George W. ..... Willard, NY
‡ Weaver, Paul H. ..... Faribault

ST. LOUIS COUNTY MEDICAL SOCIETY

Carlton, Cook, Lake and Southern portion of
St. Louis County
Regular meetings, second Thursday in each month
except July and August
Annual meeting, second Thursday in January
Number of members 203

PRESIDENT
Parson, E. Irvine ..... Duluth
SECRETARY
Thurn, Roy J. ..... Duluth
SECRETARY, EXECUTIVE OFFICE
Lundgren, Miss Margaret M. ..... Duluth
‡ Abraham, Arden L. ..... Duluth
‡ Ahrens, Curtis F. ..... Duluth
‡ Anderson, James M. ..... Duluth
Armin, David W. ..... Two Harbors
‡ Asta, Joseph J. ..... Duluth
† Athens, A. G. ..... Santa Barbara, CA
‡ Atmore, William G. ..... Duluth
‡ Aufderheide, Arthur C. ..... Duluth
Backus, Byron C. ..... Cloquet
‡ Backus, Lloyd B. ..... Cloquet
Backus, Reno W. ..... Nopeming
‡ Bagley, Charles M. ..... Duluth
Bagley, Elizabeth C. ..... Duluth
‡ Bakkila, Henry E. ..... Duluth
‡ Balmer, Albert I. ..... Duluth
*† Barney, Leon A. ..... Duluth
‡ Bartzen, Peter J. ..... Duluth
‡ Becker, Frederic T. ..... Duluth
‡ Bell, Harry M., Jr. ..... Duluth
‡ Bergan, Robert O. ..... Duluth
‡ Berns, Max H. ..... Duluth
†‡ Bianco, Anthony J. ..... Duluth
‡ Bloom, Joseph ..... Pompano Beach, FL
Blum, Clifford J. ..... Duluth
‡ Boecker, Bernhard ..... Duluth
† Boman, Paul G. ..... Duluth
‡ Boman, Peter J. ..... Duluth
‡ Boyer, Samuel H. ..... Duluth
‡ Bray, Philip N. ..... Duluth
‡ Brooker, Warren J. ..... Duluth
‡ Brown, Cyrus C., Jr. ..... Duluth
‡ Buckley, Robert P. ..... Duluth
‡ Bulluck, Matthew H. ..... Duluth
‡ Butler, John K. ..... Cloquet
‡ Campaigne, Robert J. ..... Duluth
Carter, Robert E. ..... Duluth
‡ Christensen, Clarence H. ..... Duluth
Church, Gerald E. ..... Two Harbors

St. Louis County Medical Society *(Continued)*

Clark, Elizabeth A. (Mrs. Halbert) ..... Duluth
‡ Clark, Ivan T. ..... Sun City, AZ
Clifford, Thomas M. ..... Silver Bay
‡ Coll, James J. ..... Duluth
*† Collins, Arthur N. ..... Duluth
‡ Collins, Roger T. ..... Duluth
Conley, Francis W. ..... Duluth
‡ Cotton, Gerald E. ..... Duluth
‡ Coventry, William D. ..... Duluth
‡ Cowan, Gary A. ..... Duluth
‡ Cowan, George M. ..... Duluth
‡ Creps, James R. ..... Duluth
‡ Davidson, A. Dale ..... Duluth
Davis, William ..... Moose Lake
‡ Deutsch, Robert J. ..... Duluth
‡ Dickson, Franklin H. ..... Proctor
‡ Dobbs, Richard L. ..... Duluth
‡ Drexler, Charles J. ..... Duluth
‡ Dwyer, John J. ..... Duluth
Eckman, Matthew J. ..... Duluth
‡ Eckman, Philip F. ..... Duluth
‡ Eckman, Philip L. ..... Duluth
‡ Eckman, Ralph J. ..... Duluth
‡ Ecklund, Carl D. ..... Duluth
‡ Emanuel, Karl W. ..... Duluth
‡ Engelsgjerd, Gerald L. ..... Duluth
Evison, Emerson O. ..... Duluth
Fawcett, Keith R. ..... Duluth
‡ Fellows, Manley F. ..... Duluth
‡ Feuling, John C. ..... Sun City, AZ
‡ Fifield, Malcolm M. ..... Duluth
‡ Fisketti, Henry ..... Duluth
‡ Fuller, Josiah ..... Duluth
†‡ Gillespie, Malcolm G. ..... Duluth
‡ Goldish, Daniel R. ..... Duluth
‡ Goldish, Robert J. ..... Duluth
‡ Goldschmidt, Volker ..... Duluth
‡ Goodnow, William H. ..... Duluth
‡ Gowan, Lawrence R. ..... Duluth
‡ Gowan, Lawrence R., Jr. ..... Duluth
‡ Grohs, William H. ..... Duluth
Gronquist, Y. K. J. ..... Cloquet
‡ Haavik, John E. ..... Duluth
Halbert, John J. ..... Duluth
‡ Halliday, Phillip V. ..... Duluth
Hanson, Ernest O. ..... Cloquet
Harper, David G. ..... Duluth
‡ Harrington, Vernon A. ..... Duluth
‡ Hartzell, Allan ..... Duluth
‡ Heisel, John G. ..... Duluth
Henry, Harold W. ..... Moose Lake
‡ Hilding, Anderson C. ..... Duluth
‡ Hoeg, Dwight C. ..... Duluth
‡ Hoff, Herbert O. ..... Duluth
‡ Holt, Glen E. ..... Duluth
‡ Hood, Roderick P. ..... Duluth
Houglum, Arvid J. ..... Duluth
‡ Houkom, S. Sverre ..... Duluth
† Hutchinson, Henry ..... Brainerd
Jacklin, Alexander J. ..... Duluth
‡ Jacobson, Ferdinand C. ..... Duluth
‡ Jacott, William E. ..... Duluth
*† Jensen, Thorvold J. ..... Duluth
‡ Jeronimus, Henry J. ..... Duluth
Jessico, Charles M. ..... Duluth
‡ Johnson, Franklin L. ..... Duluth
‡ Johnson, Karl E. ..... Duluth
‡ Johnson, Theodore L. ..... Duluth
‡ Juntunen, Roy R. ..... Duluth
‡ Kilen, Mark B. ..... Duluth
†‡ Klein, Harry ..... Duluth
‡ Knoedler, John P. ..... Duluth
Kosiak, William ..... Two Harbors
*‡ Krueger, Victor R. ..... Nopeming
‡ Kwako, Jerome E. ..... Duluth
‡ L'Abbe, A. J. Philip ..... Duluth
‡ LaBree, Robert H. ..... Duluth
‡ Langseth, Rodney N. ..... Duluth
‡ Larson, Donald M. ..... Duluth
Larson, Kenneth R. ..... Moose Lake
‡ Latterell, Kenneth E. ..... Duluth
‡ Leek, Joseph H. ..... Duluth
Leonardson, Peter Y. ..... Silver Bay
Leppink, Harold B. ..... Two Harbors
Leppo, N. Erkki A. ..... Duluth
‡ Linnell, Leonard S. ..... Duluth
†‡ Litman, Samuel N. ..... Duluth
†‡ McNutt, John R. ..... Duluth
MacDonald, Roger A. ..... Grand Marais
†‡ MacRae, Gordon C. ..... Duluth
† Magney, Fredolph H. ..... Duluth
Martin, Webster C. ..... Duluth
‡ Maryland, Daniel L. ..... Duluth
Mattson, Roger A. ..... Duluth
May, Horst G. ..... Duluth
‡ Mendesh, Anthony N. ..... Duluth
‡ Merrick, William G. ..... Duluth
‡ Meyer, Howard J. ..... Duluth
Michaelis, Dorothy ..... Duluth
Moller, Julie C. ..... Duluth
Monge', James J. ..... Duluth
‡ Monserud, Nels O. ..... Cloquet
‡ Moyer, John B. ..... Duluth
‡ Munger, James E. ..... Duluth
Munson, Martin S. ..... Moose Lake
‡ Myers, Thomas T., III ..... Duluth
‡ Nisius, George F. ..... Duluth
‡ Nisswandt, Albert L. ..... Duluth
† Nordberg, Carl E. ..... Los Altos, CA
‡ O'Neill, John C. ..... Duluth
‡ Parson, E. Irvine ..... Duluth
‡ Pasek, Antone W. ..... Cloquet
Patch, Orien B. ..... Duluth
*‡ Pedersen, Roy C. ..... Duluth
‡ Peterson, John H. ..... Duluth
Pollard, William S. ..... Duluth
‡ Power, John E. ..... Duluth
Puumala, Barbara M. ..... Cloquet
Puumala, Reino H. ..... Cloquet
Puumala, Ricard R. ..... Cloquet
‡ Reardon, Andrew E. ..... Duluth
‡ Reed, Henry H. ..... Duluth
‡ Rowe, Richard G. ..... Duluth
‡ Rudie, Peter S. ..... Duluth
‡ Rudie, William D. ..... Duluth
‡ Runquist, John M. ..... Duluth
‡ Ruth, Bradley R. ..... Duluth
‡ Ryan, Edward A. ..... Duluth
Sach-Rowitz, Alvan ..... Moose Lake
Saloum, Lucille M. ..... Duluth
Sandell, Samuel T. ..... Duluth
Sanford, John B. ..... Duluth
Sax, Milton H. ..... Duluth
Sax, Simon G. ..... Duluth
‡ Schmid, John F. ..... Duluth
‡ Shirley, Raymond M. ..... Duluth

Continued on Next Page

St. Louis County Medical Society *(Continued)*

Slack, William J. ..... Duluth
‡ Smith, Cyril M. ..... Duluth
Smith, Wallace R. ..... Grand Marais
† Spang, Anthony J. ..... Duluth
‡ Spang, James S. ..... Duluth
‡ Spang, William M. ..... Duluth
‡ Stein, William A. ..... Duluth
‡ Storsteen, Kenneth A. ..... Duluth
‡ Streitz, John M. ..... Duluth
‡ Strewler, Gordon J. ..... Duluth
‡ Strutton, William H. ..... Duluth
‡ Swedberg, William A. ..... Duluth
‡ Swensen, Don P. ..... Duluth
†‡ Swenson, Arnold O. ..... Duluth
Swenson, Orville P. ..... Cloquet
Teich, Kenneth W. ..... McKeesport, PA
‡ Terrell, Bernard J. ..... Nopeming
‡ Tetlie, James P. ..... Duluth
‡ Thomas, John V. ..... Duluth
‡ Thompson, James I. ..... Duluth
‡ Thurn, Roy J. ..... Duluth
‡ Tosseland, Noel E. ..... Duluth
‡ Tygart, Robert L. ..... Duluth
‡ Ulrich, Emery E. ..... Duluth
Van Druten, William A. ..... Duluth
‡ Van Puffelen, Paul S. ..... Duluth
Van Ryzin, Donald J. ..... Duluth
‡ Wahman, Robert E. ..... Duluth
‡ Walder, Harold J. ..... Duluth
‡ Wall, Jack E. ..... Duluth
‡ Wallace, Martin O. ..... Duluth
†‡ Wells, Arthur H. ..... Duluth
‡ Williams, Bruce F. P. ..... Duluth
‡ Wolfe, John W. ..... Duluth
‡ Young, Hadley R. ..... Duluth

SCOTT-CARVER COUNTY MEDICAL SOCIETY

Scott and Carver Counties
Regular meetings, first Wednesday of each month,
except July and August
Annual meeting in June
Number of members 44

PRESIDENT
Wempner, Jon D. ..... Waconia
SECRETARY
Olson, Richard E. ..... Chaska
Abrams, Donald J. ..... Shakopee
‡ Adams, Patrick J. ..... Shakopee
Amra, Waleed ..... Chaska
Bean, Charles N. ..... Waconia
Berg, John H. ..... Montgomery
‡ Bratholdt, James W. ..... Watertown
† Buck, Frederick H. ..... Shakopee
‡ Cervenka, Charles F. ..... New Prague
Clarke, John W. ..... Waconia
‡ Crislip, George D. ..... Waconia
‡ Doherty, Elmer M. ..... New Prague
Erickson, Robert L. ..... Rosemount
Gildersleeve, Robert G. ..... Watertown
‡ Hallgren, Roger B. ..... Belle Plaine
Heagle, C. Russell ..... Waconia
† Hebeinsen, Milton B. ..... Chaska
Heinz, Ivy ..... Shakopee
‡ Heinzerling, Carl R. ..... Chaska
†‡ Juergens, Herman M. ..... Belle Plaine
† Kucera, Stanley T. ..... Northfield
‡ Kuz, Eugene ..... Savage
Kvale, James N. ..... Shakopee
Larson, Leighton W. ..... Waconia
Lehmann, James D. ..... Waconia
‡ Lehrer, Alfred J., Jr. ..... Montgomery
‡ Lukk, Olaf ..... Prior Lake
† McDaniel, Samuel P. ..... Lakeville
Mendiola, Ramon P., Jr. ..... Waconia
‡ Nehring, John ..... Chaska
‡ Olson, Richard E. ..... Chaska
Palattao, Augustin D., Jr. ..... Waconia
‡ Pearson, Bror F. ..... Shakopee
‡ Philip, David R. ..... Watertown
‡ Pistulka, Rolland D. ..... Chaska
Ponterio, James E. ..... Shakopee
Provence, Cecil L. ..... Waconia
Rieschl, Elizabeth K. ..... Jordan
‡ Schimelpfenig, George T. ..... Chaska
† Smith, David G. ..... Watertown
‡ Spagnolo, Anthony A. ..... Shakopee
Stahler, Paul A. ..... Jordan
Wempner, Jon D. ..... Waconia
†‡ Westerman, Alvin E. ..... Montgomery
†‡ Westerman, Fred C. ..... Montgomery

SIBLEY COUNTY MEDICAL SOCIETY

Sibley County
Regular meetings, 3rd Monday of Odd number months
Annual meeting in November
Number of members 5

PRESIDENT
Vener, John M. ..... Arlington
SECRETARY
Knoche, Harvey A. ..... Gaylord
Bergerson, Dean ..... Arlington
Dysterheft, Adolph ..... Gaylord
† Kath, Reinhard H. ..... Merrifield
Knoche, Harvey A. ..... Gaylord
Vener, John M. ..... Arlington

SOUTHWESTERN MINNESOTA MEDICAL SOCIETY

Cottonwood, Jackson, Murray, Nobles, Pipestone and Rock Counties
Regular meetings first Monday of each month except June, July and August
Annual meeting, November
Number of members 54

PRESIDENT
Boyd, Frank ..... Pipestone
SECRETARY
Stam, John ..... Worthington

‡ Bader, Jean L. ..... Slayton
‡ Basinger, Harold P. ..... Windom
† Basinger, Homer P. ..... Windom
‡ Beckering, Gerrit ..... Edgerton
‡ Beckering, Roland G. ..... Edgerton
†‡ Benjamin, Walter G. ..... Pipestone
‡ Berner, Herbert W., Jr. ..... Worthington
†‡ Bofenkamp, Ferdinand W. ..... Luverne
‡ Boone, Ervin S. ..... Luverne
‡ Boyd, Frank E. ..... Pipestone
‡ Carlson, John V. ..... Westbrook
‡ Carlson, Lloyd E. ..... Worthington
‡ Christiansen, Harold A. ..... Jackson
‡ Dawson, Lorin D. ..... Worthington
‡ Desai, B. J. ..... Worthington
‡ Dokken, James H. ..... Windom
‡ Doman, Victor W. ..... Lakefield
‡ Eaton, David B. ..... Worthington
‡ Faul, Bennie C. ..... Worthington
‡ Fitch, Charles G. ..... Worthington
‡ Glick, Dallas D. ..... Mountain Lake
†‡ Halloran, Walter H. ..... Jackson
‡ Halpern, David J. ..... Brewster
‡ Harrison, Percy W. ..... Worthington
‡ Hegstad, Thomas C. ..... Windom
‡ Heiberg, O. M. ..... Worthington
‡ Johnson, Alan R. ..... Windom
‡ Keyes, Robert W. ..... Pipestone
†‡ Kilbride, Edwin A. ..... Worthington
‡ Kotval, Russell J. ..... Pipestone
‡ Laikola, Leslie A. ..... Adrian
‡ Lohmann, John G. ..... Pipestone
‡ Martin, Albert ..... Luverne
‡ Minge, Raymond K. ..... Worthington
‡ Mork, John N. ..... Worthington
‡ Nealy, Donald E. ..... Adrian
‡ Nywall, Dean D. ..... Slayton
‡ Odland, Donald M. ..... Luverne
‡ Patterson, Hugh D. ..... Slayton
‡ Pierce, Robert B. ..... Heron Lake
‡ Pierson, Roy F. ..... Slayton
*† Piper, William A. ..... Mountain Lake
‡ Plucker, Milton W. ..... Worthington
‡ Rud, Paul D. ..... Luverne
Ryding, Vincent ..... Ames, IA
† Schade, Frederick ..... Santa Cruz, CA
‡ Seisler, Edward P. ..... Worthington
‡ Siebert, Darrel W. ..... Luverne
‡ Stam, John ..... Worthington
‡ Strand, Jack W. ..... Jasper
†‡ Stratte, Harold C. ..... Windom
‡ Strough, LaVern C. ..... Worthington
‡ Wells, Walter B. ..... Jackson
‡ Wiens, Alvin L. ..... Mountain Lake
† Williams, Charles A. ..... Seattle, WA

STEARNS-BENTON COUNTY MEDICAL SOCIETY

Stearns and Benton Counties
Regular meetings, third Thursday of each month
Annual meeting, January
Number of members 99

PRESIDENT
Cumming, Robert J. ..... St. Cloud
SECRETARY
Espelien, Alan D. ..... St. Cloud
SECRETARY, EXECUTIVE OFFICE
Anderson, Mrs. Joyce E. ..... St. Cloud

‡ Alden, Charles W. ..... Sauk Rapids
Asp, Donald S. ..... Milaca
Aulick, Ernest J. ..... Paynesville
‡ Autrey, William A. ..... St. Cloud
‡ Ballantine, Jerome J. ..... St. Cloud
‡ Bancroft, Burton R., Jr. ..... St. Cloud
Barnett, Arthur ..... St. Cloud
Bauman, John C. ..... Foley
Baumgartner, Florian H. ..... Albany
Belshe, Joseph ..... St. Cloud
‡ Berger, Phil R. ..... St. Cloud
‡ Beuning, John B. ..... St. Cloud
‡ Bozanich, Milosh S. ..... St. Cloud
‡ Brattensborg, Henry J. ..... St. Cloud
‡ Brigham, Charles F., Jr. ..... St. Cloud
‡ Broker, Henry M. ..... St. Cloud
‡ Brown, Frank T. ..... St. Cloud
‡ Cesnik, Robert J. ..... Sauk Rapids
†‡ Clark, Harry B. ..... St. Cloud
Courteau, Robert D. ..... Playa Del Ray, CA
‡ Cress, Thomas L. ..... St. Cloud
‡ Cumming, Robert J. ..... St. Cloud
† Donaldson, Charles S. ..... St. Cloud
Dziubinski, Emil H. ..... St. Cloud
Dubois, Julian F. ..... Sauk Centre
‡ Espelien, Alan D. ..... St. Cloud
‡ Evans, Leslie M. ..... Sauk Rapids
‡ Gaida, Joseph B. ..... St. Cloud
Gerstenkorn, George B. ..... Milaca
Goehrs, Gilman H. ..... St. Cloud
Grant, John C. ..... Sauk Centre
† Halenbeck, Philip L. ..... St. Cloud
‡ Harbaugh, John T. ..... St. Cloud
‡ Held, William J. ..... St. Cloud
† Henry, Clarence J. ..... Onamia
Henry, Joseph E. ..... St. Cloud
‡ Hughes, Bernard J. ..... St. Cloud
‡ Jaeger, Dwight E. ..... St. Cloud
‡ John, Byron L. ..... St. Cloud
Johnson, Curtis A. ..... Princeton
‡ Johnson, William E. ..... St. Cloud

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Stearns-Benton County Medical Society *(Continued)*

†‡ Jones, Richard N. ..... St. Cloud
Keith, Paul J. ..... Milaca
‡ Kelly, James H. ..... St. Cloud
‡ Kelly, John F. ..... Cold Spring
Koenig, Robert P. ..... St. Cloud
‡ Koop, Severin H., Jr. ..... St. Cloud
‡ Kruzich, Stephen J. ..... St. Cloud
Kuhlmann, Lawrence B. ..... Melrose
Kvistberg, Gerald K. ..... St. Cloud
LaFond, Edward M. ..... St. Cloud
‡ Lenarz, Albert J. ..... St. Cloud
Lindeman, Raymond J. ..... Paynesville
‡ Loeb, George L. ..... St. Cloud
‡ Loes, Louis, A. ..... St. Cloud
Luby, Thomas H. ..... St. Cloud
† McDowell, John P. ..... St. Cloud
McNamara, John P. ..... Rice
‡ May, Robert B. ..... St. Cloud
† Milhaupt, Emmett N. ..... Dunedin, FL
‡ Moran, Paul T. ..... St. Cloud
Mueller, Rudolph B. ..... Richmond
‡ Murn, Thomas G. ..... St. Cloud
‡ Murray, Robert A., Jr. ..... St. Cloud
Musachio, Nicholas F. ..... St. Paul
Myre, Clifford R. ..... Paynesville
‡ Neils, Vernon E. ..... St. Cloud
Nietfield, Aloys B. ..... Sauk Centre
‡ O'Keefe, James P. ..... St. Cloud
‡ Olinger, John N. ..... St. Cloud
‡ Petersen, Robert T. ..... St. Cloud
‡ Phares, Otto C. ..... St. Cloud
‡ Raetz, Sylvester J. ..... Maple Lake
‡ Rice, William H. ..... St. Cloud
Richards, William B. ..... St. Cloud
‡ Ritchie, Donald A. ..... St. Cloud
‡ Rovelstad, Roger A. ..... St. Cloud
‡ Rozycki, Anthony T. ..... St. Cloud
Salk, Richard J. ..... Albany
Savelkoul, Gene R. ..... Belgrade
Schamber, Walter ..... St. Cloud
‡ Schmitz, Everett J. ..... St. Cloud
Sisk, Harvey E. ..... St. Cloud
‡ Slanga, Roger A. ..... St. Cloud
Smith, J. Weston ..... St. Cloud
Sommers, Stephen D. ..... St. Cloud
‡ Stahn, Louis H. ..... St. Cloud
‡ Stiles, Clifford D. ..... Foley
‡ Thienes, R. Lawrence ..... St. Cloud
‡ Thuringer, Carl B. ..... St. Cloud
Vanderpool, Thomas E. ..... Paynesville
‡ Van Nostrand, David M. ..... St. Cloud
‡ Veranth, Leonard A. ..... St. Cloud
Warner, Paul L. ..... St. Cloud
‡ Wenner, Waldemar T. ..... St. Cloud
Windschitl, Harold E. ..... St. Cloud
‡ Wittrock, Louis H. ..... Watkins
† Zachman, Albert H. ..... Melrose
‡ Zeleny, Joseph H. ..... St. Cloud

STEELE COUNTY MEDICAL SOCIETY

Steele County
Regular meetings, third Tuesday January, March, May, September and November
Annual meeting, November
Number of members 24

PRESIDENT
Honath, D. K. ..... Owatonna
SECRETARY
Benjamin, R. J. ..... Owatonna
‡ Anderson, Franklin C. ..... Owatonna
Arnesen, John F. ..... Owatonna
Benjamin, Roger J. ..... Owatonna
‡ Buresh, Kenneth L. ..... Owatonna
‡ deWerd, Robert W. ..... Owatonna
Dewey, Donald H. ..... Owatonna
Floersch, Adrian J. ..... Owatonna
‡ Halvorsen, Daniel K. ..... Owatonna
Hartung, Elmer H. ..... Claremont
‡ Henry, John C. ..... Owatonna
‡ Henry, Kenneth, G. ..... Owatonna
‡ Hilker, Robert T. ..... Owatonna
Honath, Donald H. ..... Owatonna
Kulstad, Oscar S. ..... Dodge Center
Lundquist, Curt W. ..... Owatonna
McEnaney, James E. ..... Owatonna
† McIntyre, John A. ..... Owatonna
† Morehead, Dewey E. ..... Bodega Bay, CA
Nealy, Timothy E. ..... Blooming Prairie
‡ Olson, Albert J. ..... Owatonna
† Roberts, Oliver W. ..... Owatonna
† Schaefer, Joseph F. ..... Sun City, AZ
Stransky, Theodore W. ..... Owatonna
† Wilkowske, Rudolph J. ..... Owatonna

UPPER MISSISSIPPI MEDICAL SOCIETY

Aitkin, Cass, Crow Wing, Hubbard, Morrison, Todd & Wadena Counties
Regular meetings, January, April, September
Annual meeting, January
Number of members 81

PRESIDENT
Gamm, Edgar ..... Park Rapids
SECRETARY
Anderson, Arden O. ..... Brainerd

‡ Aga, John H. ..... Brainerd
‡ Anderson, Arden O. ..... Brainerd
Belcher, Royden A. ..... Little Falls
‡ Bender, James H. ..... Brainerd
‡ Bissinger, Lester L. ..... Brainerd
‡ Borgerson, Arthur H. ..... Long Prairie
‡ Brown, Russell T. ..... Browerville
Burman, Richard E. ..... Aitkin
‡ Cardle, George E. ..... Brainerd
Closuit, Frederick C. ..... Aitkin
‡ Coombs, Carl H. ..... Cass Lake
‡ Crow, Earl R. ..... Minnetonka
† Davis, Lloyd T. ..... Wadena
Davis, Luther F. ..... Wadena
Dimmick, Ivan C. ..... Brainerd
†‡ Erickson, Alvin O. ..... Long Prairie
‡ Fitzsimons, William E. ..... Brainerd
Fortier, George M. A. ..... Little Falls
‡ Fortier, George M. A., Jr. ..... Little Falls
Gamm, Edgar R. ..... Park Rapids
† Ghostley, Mary C. ..... Minneapolis
‡ Grimes, Paul T. ..... Park Rapdis
‡ Grose, Frederick N. ..... Clarissa
Halme, William B. ..... Wadena
Hansen, Milo L. ..... Little Falls
Heid, James K. ..... Little Falls
Hildreth, Thomas A. ..... San Francisco, CA
Jacobson, Dennis ..... Onamia
‡ Johnson, Douglas L. ..... Brainerd
‡ Kanne, Earl R. ..... Brainerd
‡ Kelley, Roger E. ..... Crosby
Knipp, William J. ..... Brainerd
†‡ Knoll, W. V. ..... Brainerd
‡ Kussy, James C. ..... Little Falls
Larson, Donald R. ..... Crosby
‡ Larson, Theodore G. ..... Brainerd
‡ Lee, Hubert W. ..... Brainerd
‡ Lelwica, Thaddeus J. ..... Staples
‡ Lofstrom, Dennis E. ..... Brainerd
Longfellow, Helen W. ..... Brainerd
† Lund, Werner J. ..... Staples
‡ McLane, William O. ..... Brainerd
‡ Marshall, Clark M. ..... Crosby
‡ Marvin, Joseph E. ..... Brainerd
‡ Meller, Maurice ..... Brainerd
‡ Mennis, William I. ..... Staples
‡ Mortenson, Howard O. ..... Menahga
‡ Mosby, Maurice E. ..... Long Prairie
‡ Mulligan, Arthur M. ..... Brainerd
‡ Muus, John H. ..... Staples
Ness Duane E. ..... Wadena
‡ Nixon, James B. ..... Crosby
Nordberg, Robert J. ..... Little Falls
Nordlund, Mildred E. ..... Carmichael, CA
Olson, Lillian A. ..... Ah-Gwah-Ching
‡ Parker, Warren E. ..... Sebeka
‡ Pedersen, Robert L. ..... Brainerd
‡ Pelzl, Charles R. ..... Pine River
Petraborg, Harvey T. ..... Aitkin
Petterson, George R. ..... Aitkin
‡ Poppie, Robert W. ..... Brainerd
‡ Reichelderfer, Charles ..... Staples
‡ Reichelt, Leland G. ..... Wadena
†‡ Ringle, Otto F. ..... Walker
‡ Scanlon, Hugh A. ..... Little Falls
Schulberg, Verne A. ..... Minneapolis
‡ Seifert, Donald R. ..... Little Falls
Soriano, Dominador B. ..... Onamia
Spieler, F. B. ..... Pequot Lakes
†‡ Stein, Raymond J. ..... Pierz
‡ Stoy, Robert A. ..... Little Falls
Terrian, James C. ..... Walker
‡ Thompson, V. James ..... Staples
‡ Vandersluis, Charles W. ..... Minneota
‡ Watson, Sidney W. ..... Little Falls
‡ Westley, Kent F. ..... Little Falls
‡ Wiger, Oliver E. ..... Little Falls
‡ Williams, Mervyn M. ..... Ah-Gwah-Ching
‡ Witter, Robert L. ..... Wadena

WABASHA COUNTY MEDICAL SOCIETY

Wabasha County
Regular meetings, special call
Annual meeting first Thursday after first Monday in October
Number of members 11

PRESIDENT
Timm, Marvin E. ..... Wabasha
SECRETARY
Bowers, R. N. ..... Lake City

‡ Bouquet, Bertram J. ..... Wabasha
‡ Bowers, Robert N. ..... Lake City
‡ Ellis, Earl W. ..... Elgin
Feigal, Gary R. ..... Lake City
‡ Gjerde, William P. ..... Lake City
† Habein, Harold C. ..... Palo Alto, CA
‡ Mahle, Donald G. ..... Wabasha
Moline, Doreen Martin ..... Pepin, WI
*† Ochsner, Clarence G. ..... Santa Barbara, CA
† Replogle, William H. ..... Eugene, OR
‡ Sontag, David W. ..... Lake City
Timm, Marvin E. ..... Wabasha

WASECA COUNTY MEDICAL SOCIETY

Waseca County
Regular meeting, January
Annual meeting, January
Number of members 6

PRESIDENT
Hottinger, R. C. ..... Janesville
SECRETARY
Hergott, Patrick ..... Waseca
Davis, Raymond D. ..... Stockton, CA
‡ Hergott, Patrick ..... Waseca
‡ Hottinger, Raymond C. ..... Janesville
‡ Normann, Stephen T. ..... Waseca
‡ Oeljen, S. C. G. ..... Waseca
‡ Olds, George H. ..... New Richland
* Swenson, Orvie J. ..... Waseca

WASHINGTON COUNTY MEDICAL SOCIETY

Washington and Dakota Counties
Regular meetings, first Tuesday in each month
Annual meeting, June
Number of members 30

PRESIDENT
Peterson, John O. H. ..... Hastings
SECRETARY
Zeller, Hector ..... Hastings
Bealka, Neil ..... Stillwater
† Brabec, Paul F. ..... Hastings
Canine, James L. ..... So. St. Paul
Dale, Les N. ..... Hastings
‡ deLeon, Ben ..... Stillwater
Diessner, Ardell W. ..... Stillwater
† Eiden, Vera M. ..... Stillwater
Fasbender, Herman T. ..... Hastings
Foderick, John W. ..... Hastings
† Holcomb, Joel T. ..... Marine-on-the-St. Croix
Hunter, Murray H. ..... Farmington
‡ Jenson, James E. ..... Stillwater
Johnson, O. Guy ..... St. Paul
‡ Juergens, Manley F. ..... Stillwater
† Just, Herman J. ..... Hastings
Kiolbasa, Edward B. ..... Stillwater
Kulzer, Norbert J. ..... Hastings
‡ McCarten, Francis M. ..... Stillwater
Midboe, Gilbert T. ..... Forest Lake
‡ Murphy, Thomas R. ..... Stillwater
Peikert, Carl F. ..... Forest Lake
Peterson, John O. H. ..... Hastings
Purdie, James ..... Forest Lake
Ruggles, George M. ..... Forest Lake
Schulz, Jerome E. ..... Stillwater
Schwartz, Carl ..... Hastings
† Sherman, Carnot H. ..... Bayport
‡ Stratte, Jon R. ..... Stillwater
† Van Meier, Henry ..... Stillwater
Weiss, Carl A. ..... Hastings
Zeller, Hector ..... Hastings

WEST CENTRAL MINNESOTA MEDICAL SOCIETY

Big Stone, Pope, Stevens and Traverse Counties
Regular meetings, third Tuesday in March, May, September and November
Annual meeting, November
Number of members 22

PRESIDENT
Rossberg, R. A. ..... Morris
SECRETARY
Popoff, Russel G. ..... Graceville
Benjamin, Charles I. ..... Glenwood
† Bergan, Otto ..... Clinton
Brace, Ray I. ..... Clinton
Bucher, Foster D. ..... Starbuck
† Christenson, Carl E. ..... Clinton
Colago, Victor M. ..... Browns Valley
Eide, O. A. ..... Hancock
Hedemark, Homer H. ..... Ortonville
† Hedemark, Truman A. ..... Ortonville
Karn, Jacob F. ..... Ortonville
Knip, Robert J. ..... Ortonville
‡ Kolp, Berton A. ..... Glenwood
Kooda, Jennings C. ..... Morris
Kozel, William J. ..... Morris
Lee, Gordon E. ..... Glenwood
Magnuson, Allen E. ..... Fargo, ND
Merrill, Robert ..... Des Moines, IA
Popoff, Russel G. ..... Garceville
Rossberg, Raymond A. ..... Morris
Swedenburg, Paul A. ..... Glenwood
Watson, Robert M. ..... Morris
Winge, H. C. ..... Wheaton
Zempel, Alan R. ..... Starbuck

WINONA COUNTY MEDICAL SOCIETY

Winona County
Regular meetings, second Tuesday in January, April, July and October
Annual meeting, January
Number of members 34

PRESIDENT
Finkelnburg, W. O. ..... Winona
SECRETARY
Heise, Herbert vR. ..... Winona
‡ Andersen, Horace J. ..... Winona
‡ Boardman, Dalmon V. ..... Winona
Bunnell, Harris F. ..... Winona
†‡ Christensen, Eli E. ..... Winona
‡ Degallier, Daniel ..... Winona
Edin, Andrew E. ..... Winona
‡ Fenske, Arnold ..... Winona
Finkelnburg, William ..... Winona
‡ Garber, George L. ..... Winona
‡ Haesly, Warren W. ..... Winona
‡ Hartwich, Roger F. ..... Winona
‡ Hawk, Dale J. ..... St. Charles
Heise, Carl vR. ..... Winona
‡ Heise, Herbert vR. ..... Winona
‡ Heise, Paul vR. ..... Winona
‡ Heise, William vR. ..... Winona
Herland, Alexander L. ..... Winona
Hick, John F. ..... Winona
‡ Hughes, Sidney O. ..... Winona
‡ Johnson, Curtis M. ..... Winona
‡ Johnston, Leonard ..... Winona
‡ Loomis, George L. ..... Winona
† Meinert, Albert E. ..... Winona
Miller, Linda K. ..... Winona
‡ Peterson, John R. ..... Rushford
‡ Roemer, Henry J. ..... Winona
‡ Rogers, Charles W. ..... Winona
‡ Schafer, Charles F. ..... Winona
† Schmidt, Hilmer R. ..... Winona
Tweedy, John A. ..... Winona
‡ Tweedy, Robert B. ..... Winona
Vieiralves, G. M. ..... Winona
Wilson, L. J. ..... Rushford
† Wilson, R. H. ..... Winona

WRIGHT COUNTY MEDICAL SOCIETY

Wright County
Regular meetings, first Tuesday of every other month
Annual meeting in November
Number of members 17

PRESIDENT
Sandeen, Robert M. ..... Buffalo
SECRETARY
Bentzin, Clyde ..... Monticello
‡ Anderson, Waldo P. ..... Buffalo
‡ Bendix, Lester H. ..... Annandale
‡ Bentzin, C. K. ..... Monticello
‡ Catlin, Theodore J. ..... Buffalo
†‡ Ellison, Frank E. ..... Monticello
‡ Guilfoile, Pierre J. ..... Delano
†‡ Hart, William E. ..... Monticello
‡ Maus, Donald J. ..... Monticello
‡ Ourada, Anthony L. ..... Buffalo
‡ Purves, G. Harland ..... Buffalo
‡ Sandeen, Robert M. ..... Buffalo
‡ Shin, Rok ..... Howard Lake
‡ Smorstok, Matthew B. ..... Monticello
‡ Steiner, Andrew M. ..... St. Michael
†‡ Thielen, R. D. ..... New Brighton
‡ Whitesell, L. A., Jr. ..... Buffalo
‡ Zapf, John D. ..... Monticello

ZUMBRO VALLEY MEDICAL SOCIETY

Olmsted, Houston, Fillmore and Dodge Counties
Regular meetings, first Wednesday of every odd-numbered month
Annual meeting, November
Number of members 831

PRESIDENT
Doyle, James R. ..... Rochester
SECRETARY
Tyce, Francis A. ..... Rochester
EXECUTIVE SECRETARY
Fricke, Robert E. ..... Rochester
‡ Aaro, Leonard A. ..... Rochester
† Abbound, Charles F. ..... Rochester
† Adkins, William C. ..... Rochester
‡ Adson, Martin A. ..... Rochester
‡ Affeldt, Daniel E. ..... Kasson
† Ahlfs, Jacob J. ..... Ft. Lauderdale, FL
‡ Ahmann, David L. ..... Rochester
*† Amberg, Samuel ..... Rochester
‡ Andersen, Howard A. ..... Rochester
‡ Anderson, Carl F. ..... Rochester
† Anderson, James A. ..... Rochester
† Anderson, Mark J. ..... Sun City, AZ
‡ Anderson, Markham J., Jr. ..... Rochester
† Anderson, Michael D. ..... Rochester
‡ Anderson, Milton W. ..... Rochester
† Anderson, Richard D. ..... Rochester
Andreini, Paul H. ..... Rochester
† Applestein, Bruce ..... Rochester
† Arena, Paul J. ..... Rochester
Ashby, Thomas M. ..... Loma Linda, CA
‡ Baars, Conrad W. ..... Rochester

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Zumbro Valley Medical Society *(Continued)*

‡ Baggenstoss, Archie H. ..... Rochester
†‡ Bair, Hugo L. ..... Rochester
Baird, Raymond L. ..... Reno, NV
¶ Bajec, Dusan ..... Belgrade, Yugoslavia
‡ Baker, George S. ..... Rochester
† Baker, Harry R. ..... Hayfield
‡ Baker, Hillier L., Jr. ..... Rochester
Balfour, William M. ..... Lawrence, MO
‡ Banfield, Frederick D. ..... Rochester
‡ Banner, Edward A. ..... Rochester
Baran, Frnest M. ..... Beaver Meadows, PA
Barbee, Charles W. ..... Rochester
‡ Barry, Maurice, J., Jr. ..... Rochester
‡ Bartholomew, Lloyd G. ..... Rochester
‡ Bastron, James A. ..... Rochester
Baumer, Robert J. ..... Rochester
‡ Bayrd, Edwin D. ..... Rochester
‡ Beabout, John W. ..... Rochester
‡ Beahrs, Oliver H. ..... Rochester
Bean, William J. ..... Rochester
Bechamps, Gerald J. ..... Fort Eustis, VA
† Beckenbaugh, Robert D. ..... Rochester
† Becker, Paul W. ..... Rochester
† Beckley, James M. ..... Rochester
Beeckler, Donald C. ..... Rochester
‡ Belau, Paul G. ..... Rochester
‡ Bennett, Clayton J. ..... Rochester
† Benson, Ralph C., Jr. ..... Rochester
‡ Berge, Kenneth G. ..... Rochester
†‡ Berkman, John M. ..... Rochester
† Berman, Stanley Z. ..... Rochester
† Bernstein, Sidney S. ..... Rochester
† Besson, Augustin ..... Rochester
Beuret, Lawrence J. ..... Rochester
† Beyerlein, Charles R. ..... Rochester
‡ Bianco, Anthony J., Jr. ..... Rochester
‡ Bickel, William H. ..... Rochester
† Birkemeyer, Eugene J. ..... Rochester
‡ Bisel, Harry F. ..... Rochester
‡ Black, B. Marden ..... Rochester
‡ Black, Leo F. ..... Rochester
† Blanco-Benavides, Roberto ..... Rochester
† Blume, Warren T. ..... Rochester
Bonebrake, Robert A. ..... Gurnee, IL
† Bonfil-Roberts, Enrique A. ..... Rochester
†‡ Boyd, David A., ... Rochester
† Boyer, Andrew G. ..... Rochester
† Braasch, William F. ..... Rochester
‡ Brandenburg, Robert O. ..... Rochester
† Breivis, James S. ..... Rochester
Brewster, Robert C. ..... Grand Forks, ND
† Brinkman, James F. ..... Rochester
‡ Brodhun, John C. ..... Rochester
† Brown, Alan P. ..... Rochester
† Brown, Alex E. ..... Bradenton, FL
‡ Brown, Arnold L. ..... Rochester
‡ Brown, Henry A. ..... Rochester
‡ Brown, Joe R. ..... Rochester
†‡ Brown, Philip W. ..... Rochester
‡ Brown, Philip W., Jr. ..... Rochester
† Brown, Stephen R. ..... Rochester
Brubaker, Richard F. ..... Rochester
† Bryan, James W. ..... Rochester
‡ Bryan, Richard S. ..... Rochester
† Buckley, John P. ..... Rochester
† Buie, Louis A. ..... Rochester
† Bunch, Thomas W. ..... Rochester
† Buntain, William L. ..... Rochester
‡ Burgert, E. O., Jr. ..... Rochester
† Burgess, John N. ..... Rochester
‡ Burich, Harry F. ..... Rochester
‡ Burke, Edmund C. ..... Rochester
† Burns, Jess R. ..... Rochester
† Bush, David J. ..... Rochester
‡ Butt, Hugh R. ..... Rochester
† Buza, Robert C. ..... Rochester
† Buzanowski, Krystyna ..... Rochester
† Byer, David E. ..... Rochester
† Cabanela, Miguel E. ..... Rochester
‡ Cain, James C. ..... Rochester
‡ Callahan, John A. ..... Rochester
† Camacho, Luis-Guillermo ..... Rochester
Cameron, Alan J. ..... Rochester
† Campa, Herman K. ..... Rochester
‡ Campbell, Donald C. ..... Rochester
† Campbell, John T. ..... Rochester
‡ Campbell, Malcom K. ..... Rochester
† Cangemi, Francis E. ..... Rochester
† Cannon, Patrick J. ..... Rochester
† Carder, George A. ..... Rochester
‡ Carlson, Harley C. ..... Rochester
Carnahan, Charles E. ..... Grandview, MO
Carney, Francoise ..... Rochester
Carr, David T. ..... Rochester
‡ Carryer, Haddon M. ..... Rochester
‡ Carter, Earl T. ..... Rochester
† Cassan, Stanley T. ..... Rochester
† Cheng, Vincent S. T. ..... Rochester
Chesebro, James H. ..... Rochester
† Chidlow, Judd H. ..... Rochester
‡ Childs, Donald S., Jr. ..... Rochester
† Ching, Ernesto ..... Rochester
‡ Christensen, Norman A. ..... Rochester
Chumbley, Lee C. ..... Rochester
† Chychota, Norman N. ..... Rochester
‡ Clagett, O. Theron ..... Rochester
† Clark, Edward C. ..... San Francisco, CA
† Clark, Leslie W. ..... Manchester, IA
† Cloherty, Martin G. ..... Rochester
‡ Code, Charles F. ..... Rochester
‡ Cody, D. Thane ..... Rochester
† Cody, Michael C. ..... Rochester
† Cohen, Manley ..... Long Beach, CA
‡ Colby, Malcolm Y., Jr. ..... Rochester
† Coleman, Robert L. ..... Rochester
‡ Coles, Douglas T. ..... Rochester
† Colville, David S. ..... Rochester
Conn, Richard L. ..... Albuquerque, NM
‡ Connolly, Daniel C. ..... Rochester
† Connor, Ann C. S. ..... Rochester
†‡ Cook, Edward N. ..... Rochester
† Cooper, Herbert A. ..... Rochester
‡ Cooper, Talbert ..... Rochester
† Cooperman, Avram M. ..... Rochester
‡ Corbin, Kendall B. ..... Rochester
† Corrado, Angelini ..... Rochester
Corrigan, Cyril J. ..... Rochester
‡ Coventry, Markham B. ..... Rochester
† Crowder, David F. ..... Rochester
† Cullen, Joseph M. ..... Rochester
‡ Culp, Clyde E. ..... Rochester
‡ Culp, Ormond S. ..... Rochester
Cupps, Roger E. ..... Rochester
‡ Dahlin, David C. ..... Rochester
‡ Dale, Allan J. D. ..... Rochester
† Daniel, William W., Jr. ..... Rochester
† Datnow, Boris ..... Rochester
‡ Daugherty, Guy W. ..... Rochester
Dauphine, Richard T. ..... FPO, NY, NY

Zumbro Valley Medical Society *(Continued)*

† Davis, Austin C. ..... Pompano Beach, FL
† Davis, David L. ..... Rochester
‡ Davis, George D. ..... Rochester
† Davis, Zev ..... Rochester
‡ Dearing, William H. ..... Rochester
‡ Decker, David G. ..... Rochester
† Deffner, Norman F. ..... Rochester
Deger, Grant E. ..... Fairchild AFB, WA
‡ DeRemee, Richard A. ..... Rochester
De Santo, Lawrence W. ..... Rochester
† de Souza e Silva, Nelson A. ..... Rochester
Detenbeck, Lee C. ..... Rochester
‡ Devine, Kenneth D. ..... Rochester
Devloo, Robert A. ..... Rochester
‡ DeWeerd, James H. ..... Rochester
‡ Didier, Edward P. ..... Rochester
‡ Diessner, G. Roy ..... Rochester
† DiPasquale, Joseph A. ..... Rochester
† Disney, Thomas F. ..... Rochester, NY
† Djalilian, Mohsen ..... Rochester
† Dobes, William L., Jr. ..... Rochester
† Dobmeier, Lawrence J. ..... Rochester
‡ Dobyns, James H. ..... Rochester
‡ Dockerty, Malcom B. ..... Rochester
† Donoghue, Edmund R., Jr. ..... Rochester
‡ Donoghue, Francis E. ..... Rochester
‡ Douglass, Bruce E. ..... Rochester
† Downey, Gale T. ..... Rochester
Doyle, James R. ..... Rochester
† Dozois, Roger R. ..... Rochester
† Drips, Della G. ..... Rochester
† Driscoll, Thomas P. ..... Rochester
† Dube, William J. ..... Rochester
† DuBoff, Stuart M. ..... Rochester
† DuBois, David D. ..... Rochester
† Dunham, Tom R. ..... Rochester
† Dupree, Emmett L., Jr. ..... Rochester
† Durie, Brian G. M. ..... Rochester
‡ Dyck, Peter J. ..... Rochester
‡ Dyer, John A. ..... Rochester
Eckelberg, Merlyn E. ..... Fort Clayton, Canal Zone
† Eckstein, John D. ..... Rochester
† Edwards, Walter G., Jr. ..... Atlanta, GA
† Egan, Ernest L. ..... Rochester
†‡ Elkins, Earl C. ..... Rochester
† Ellerby, Richard A. ..... Rochester
† Elliott, Frederick W. ..... Rochester
† El Shahawy, Mahfouz A. ..... Rochester
Emerson, Robert K. ..... Laredo, TX
† Emmett, John L. ..... Rochester
† Emmons, Patricia R. ..... Rochester
† Emmons, W. Frank ..... Vancouver, B.C., Canada
Engel, Andrew G. ..... Rochester
† Engels, Edward P. ..... Marshall
† Engelberg, Jerry ..... Rochester
‡ Erich, John B. ..... Rochester
‡ Erickson, Donald J. ..... Rochester
† Erwin, Donald T. ..... Rochester
‡ Espinosa, Raul E. ..... Rochester
† Ettinger, David S. ..... Rochester
† Etzell, Paul S. ..... Rochester
† Evans, Titus C., Jr. ..... Rochester
‡ Faber, John ..... Rochester
Facer, George W. ..... Rochester
† Farrell, Kenneth H. ..... Rochester
‡ Farrow, George M. ..... Rochester
‡ Faulconer, Albert, Jr. ..... Rochester
Fay, Thomas M. ..... Oakland, CA
† Fehrenbaker, Lawrence G. ..... Rochester
† Feinberg, Jack H. ..... Rochester
† Feintuck, Theodore A. ..... Rochester
Feldmann, Floyd M. ..... Pompano Beach, FL
‡ Ferguson, Richard H. ..... Rochester
‡ Ferris, Deward O. ..... Rochester
Fink, Lawrence H. ..... Rochester
† Fink, Richard A. ..... Rochester
‡ Fish, Charles R. ..... Rochester
† Fitz, Frederick W. ..... Rochester
† Fitzgerald, Robert H., Jr. ..... Rochester
† Fitzpatrick, Patrick J. ..... Rochester
Flanigan, Donald J. ..... Pensacola, FL
† Fleming, Martin P. ..... Rochester
Flick, William F. ..... Rochester
† Foley, Thomas F. ..... Salt Lake City, UT
‡ Fontana, Robert S. ..... Rochester
Forker, Alan D. ..... Coronado, CA
† Foss, Edward L. ..... Condon, MT
† Foster, Thomas N., III ..... Rochester
‡ Foulk, William T., Jr. ..... Rochester
Fowler, Franklin S., Jr. ..... San Francisco, CA
Fox, John A. ..... Fort Dix, NJ
Freel, Robert J. ..... Lackland AFB, TX
† Freedman, Harvey M. ..... Rochester
† Freeman, Richard E. ..... Rochester
‡ Frethem, Allen A. ..... Rochester
† Fricke, Robert E. ..... Rochester
Frytak, Stephen ..... Rochester
† Fuller, Edwin B. ..... Rochester
‡ Furlow, William L. ..... Rochester
† Furzyfer, Jacob ..... Mexico
Galloway, Jackson R. ..... Alexandria, LA
†‡ Gambill, Carl M. ..... Rochester
‡ Gambill, Earl E. ..... Rochester
‡ Garber, James J. ..... Rochester
Garrick, James G. ..... Bethesda, MD
‡ Gastineau, Clifford F. ..... Rochester
Gentling, Peter A. ..... San Diego, CA
‡ Geraci, Joseph E. ..... Rochester
† Gerstner, Phillip L. ..... Rochester
† Gifford, William A. ..... Rochester
Gildersleeve, John W. ..... Ashland, WI
‡ Gisvold, John J. ..... Rochester
† Goellner, John R. ..... Rochester
‡ Goldstein, Norman P. ..... Rochester
‡ Goldston, Edgar ..... Rochester
‡ Good, C. Allen, Jr. ..... Rochester
† Goodwin, Henry N. ..... Rochester
‡ Gorman, Colum A. ..... Rochester
‡ Gould, Allan B., Jr. ..... Rochester
† Gould, Barry K. ..... Rochester
† Gould, Ronauld J. ..... Rochester
Grabow, Jack D. ..... Rochester
† Graf, John A. ..... Rochester
† Gran, Gary E. ..... Rochester
Gravett, Desmond C. ..... Rochester
‡ Green, Paul A. ..... Rochester
‡ Greene, Laurence F. ..... Rochester
Griffiths, Robert W. ..... El Paso, TX
‡ Groover, Robert V. ..... Rochester
‡ Gross, John B. ..... Rochester
Grubbs, Larry T. ..... Rochester
† Gunderson, David H. ..... Rochester
† Haakenson, Robert C. ..... Rochester
† Hable, Kathleen A. ..... Rochester
† Haddad, Nickie J. ..... Rochester
† Haddad, Paul G. ..... Indianapolis, IN
‡ Hagedorn, Albert B. ..... Rochester
‡ Hahn, Frederick W., Jr. ..... Rochester

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Zumbro Valley Medical Society *(Continued)*

‡ Hahn, Richard G. ..... Rochester
†‡ Haines, Samuel F. ..... Rochester
†‡ Hallberg, Olav E. ..... Rochester
Ham, Oscar E., Jr. ..... Savannah, GA
† Hammargren, Lonnie L. ..... Rochester
† Hancock, William E. ..... Rochester
‡ Hanlon, David G. ..... Rochester
† Hanson, Norbert O. ..... Rochester
† Harbold, Norris B., Jr. ..... Rochester
† Harder, Edward J. ..... Rochester
†‡ Hargraves, Malcolm M. ..... Rochester
† Harrington, Stuart W. ..... Rochester
‡ Hartfield, James E., Jr. ..... Rochester
Havig, Terrance A. ..... Lubbock, TX
† Hayashi, Melvin M. K. W. ..... Rochester
‡ Hayles, Alvin B. ..... Rochester
Hays, James C. ..... APO, NY
† Heck, Frank J. ..... Rochester
† Heidel, Werner ..... Cresskill, NJ
† Heinberg, Charles E. ..... Rochester
† Heinzer, Francois C. ..... Rochester
† Helgason, Pall B. ..... Rochester
‡ Helmholz, Henry F., Jr. ..... Rochester
‡ Henderson, Edward D. ..... Rochester
‡ Henderson, John W. ..... Rochester
‡ Henderson, Lowell L. ..... Rochester
† Hendricks, John L. ..... Rochester
Henke, Clarence E. ..... Rochester
‡ Hepper, Norman G. ..... Rochester
† Herman, Peter S. ..... Rochester
‡ Hermans, Paul E. ..... Rochester
† Hewitt, Edith S. ..... Rochester
*† Hewitt, Richard M. ..... Rochester
‡ Hill, John R. ..... Rochester
‡ Hill, Richard W. ..... Rochester
† Hill, Wayne A. ..... Rochester
† Hiller, Erhard ..... Rochester
Hines, Edgar A., Jr. ..... Brevard, NC
Hoagland, H. Clark ..... Rochester
‡ Hodgson, John R. ..... Rochester
† Hodgson, Stephen F. ..... Rochester
† Hoehn, James G. ..... Rochester
Holbrook, Margaret A. ..... Rochester
Holland, C. R. ..... Rochester
‡ Hollenhorst, Robert W. ..... Rochester
† Holm, Jan ..... Rochester
‡ Holman, Colin B. ..... Rochester
‡ Hoover, Norman W. ..... Chicago, IL
†‡ Horton, Bayard T. ..... Rochester
‡ Houser, Otis W. ..... Rochester
‡ Howard, Frank M., Jr. ..... Rochester
† Howard, John D. ..... Rochester
‡ Howell, Llewelyn P. ..... Rochester
† Hu, Chung Hong ..... Rochester
† Hudson, Albert W. ..... Rochester
† Huerta, Enrique ..... Rochester
‡ Hunder, Gene G. ..... Rochester
† Hunt, Arthur B. ..... Carmel, CA
‡ Hunt, James C. ..... Rochester
† Hutchinson, James C., Jr. ..... Rochester
† Hynes, Kieran M. ..... Rochester
† Hyslopp, Thomas ..... Rochester
† Ireland, Damian C. R. ..... Rochester
Isaacson, Ronald ..... Mather, AFB, CA
‡ Ivins, John C. ..... Rochester
‡ Jackman, Raymond J. ..... Rochester
† Jackson, Charles B. ..... Rochester
Janda, Wayne E. ..... Austin, TX
† Jander, Hartwig P. ..... Rochester
‡ Janes, Joseph M. ..... Rochester
† Jensen, James W. ..... Rochester
† Jilek, Dennis D. ..... Rochester
‡ Johnson, Carl E. ..... Rochester
† Johnson, Charles L. ..... Rochester
‡ Johnson, Einer W., Jr. ..... Rochester
† Johnson, Gerhard J. ..... Rochester
† Johnson, Kenneth A. ..... Rochester
Johnson, Ralph B. ..... Lanesboro
Johnson, Thomas F. ..... Orlando, FL
† Johnson, Warren L., Jr. ..... Rochester
‡ Johnson, William J. ..... Rochester
Jones, Allen M. ..... San Angelo, TX
† Jones, H. Royden, Jr. ..... Rochester
† Jordan, James J. ..... Rochester
Jorgensen, Edward D. ..... Rochester
Joy, William B. ..... San Diego, CA
‡ Joyce, John W. ..... Rochester
‡ Judd, Edward S. ..... Rochester
† Juncos, Luis I. ..... Rochester
† Juttner, Hans-Udo ..... Rochester
‡ Kaese, Werner E. ..... Rochester
† Kantack, Paul W. ..... Rochester
‡ Karnes, William E. ..... Rochester
† Karsell, Philip R. ..... Rochester
Katz, Elliott S. ..... Phoenix, AZ
‡ Kazmier, Francis J. ..... Rochester
† Kearney, R. Wynn Jr. ..... Rochester
‡ Kearns, Thomas P. ..... Rochester
†‡ Keith, Haddow M. ..... Rochester
† Keith, Norman M. ..... Rochester
Kelalis, Panayotis P. ..... Rochester
‡ Kelly, Patrick J. ..... Rochester
† Kelman, Donald B. ..... Rochester
‡ Kennedy, Charles C. ..... Rochester
†‡ Kernohan, James W. ..... Rochester
‡ Kerr, Frederick W. L. ..... Rochester
† Keys, Thomas F. ..... Los Angeles, CA
‡ Kiely, Joseph M. ..... Rochester
‡ Kierland, Robert R. ..... Rochester
† Killean, James E. ..... Rochester
† Kim, Hyun-Hahk ..... Rochester
‡ Kimmel, George E. ..... Rochester
Kinca, Owings W. ..... Rochester
King, John E. ..... Ft. Worth, TX
† Kipfer, Robert E. ..... Rochester
‡ Kirby, Thomas J. ..... Rochester
† Kirchner, Arthur B. ..... Rochester
Kirklin, John W. ..... Birmingham, AL
Klass, Donald W. ..... Rochester
Knapp, Robert D., Jr. ..... Rochester
‡ Knutson, Lewis A. ..... Spring Grove
† Kondo, Kiyotaro ..... Rochester
‡ Konicek, Robert G. ..... Rochester
† Kopp, James E. ..... Rochester
† Koppers, Lawrence E. ..... Rochester
Krigsten, Eli J. ..... Weisbaden, Germany
† Krohn, John R. ..... Rochester
‡ Krupp, Neal E. ..... Rochester
† Kruse, Robert L. ..... Rochester
Kubista, Theodore P. ..... San Diego, CA
† Kuers, Peter F. W. ..... Rochester
† Kuge, Mark T. ..... Rochester
† Kuglitsch, John F. ..... Rochester
† Kuster, Gustavo, G. R. ..... Rochester
* Kvale, Walter F. ..... Rochester
Kvamme, Brynjulv ..... Mable
‡ Kyle, Robert A. ..... Rochester
† Laflamme, Georges-Henri ..... Rochester

Zumbro Valley Medical Society *(Continued)*

‡ Lake, Clifford F. ..... Rochester
† Lantz, James P. ..... Rochester
† Laster, Charles E. ..... Rochester
† Laventman, Jaime ..... Rochester
† Lawrence, Robert B. ..... Rochester
Layton, Donald D., Jr. ..... Rochester
Leary, Frank J. ..... Rochester
Leavelle, Dennis E. ..... San Antonio, TX
‡ Lee, Raymond A. ..... Rochester
‡ Lee, Robert E. ..... Rochester
‡ Leonard, Paul F. ..... Rochester
† Levy, Jonathan M. ..... Rochester
† Lie, Jauw, Tjen ..... Rochester
‡ Lillie, John C. ..... Rochester
‡ Lindsay, Malcolm I., Jr. ..... Rochester
‡ Linman, James W. ..... Rochester
† Lippman, Harry H. ..... Rochester
†‡ Litin, Edward M. ..... Hopkins
‡ Litzow, Thaddeus J. ..... Rochester
‡ Lofgren, Eric P. ..... Rochester
‡ Lofgren, Karl A. ..... Rochester
‡ Logan, George B. ..... Rochester
Long, John C. ..... Chicopee Falls, MA
Longstreth, George F. ..... Rochester
Loos, Gerald D. ..... APO New York, NY
†‡ Love, J. Grafton ..... Rochester
‡ Ludes, Bernard F. ..... Rochester
† Lund, Richard E. ..... Rochester
‡ Lynn, Hugh B. ..... Rochester
‡ McBean, James B. ..... Rochester
† McBurney, P. Louis ..... Rochester
† McCann, William D. ..... Rochester
‡ McConahey, William M., Jr. ..... Rochester
† McDonald, Thomas J. ..... Rochester
† McDuffie, Richard W., Jr. ..... Rochester
† McElfresh, Edward C. ..... Rochester
McGee, Hugh E., Jr. ..... Rochester
‡ McGill, Douglas B. ..... Rochester
‡ McIlrath, Donald C. ..... Rochester
† McIlroy, Gary T. ..... Rochester
† McIntyre, Donald G. ..... Rochester
#‡ McKenna, Charles H. ..... Rochester
† McKinne, Richard A. ..... Rochester
McLaughlin, Richard P. ..... Minot, ND
‡ MacCarty, Collin S. ..... Rochester
† MacDade, Albert D. ..... Rochester
† MacDonald, Charles J. ..... Rochester
† MacDonald, Vance D. ..... Rochester
MacLean, Alexander R. ..... Rochester
†‡ Magath, Thomas B. ..... Rochester
Magid, Gail A. ..... Santa Cruz, CA
‡ Maher, Frank T. ..... Rochester
† Maish, George O., Jr. ..... Rochester
† Malek, Reza S. ..... Rochester
‡ Malkasian, George D. ..... Rochester
‡ Mankin, Harold T. ..... Rochester
† Manson, Roberto R. ..... Rochester
‡ Marcoux, J. Paul ..... Rochester
† Margie, Robert P. ..... Rochester
† Marik, Francis ..... Rochester
† Marion, Dennis F. ..... Rochester
Martalock, Dean L. ..... Great Lakes, IL
‡ Martens, Theodore G. ..... Rochester
† Martimbeau, Pierre ..... Rochester
‡ Martin, Gordon M. ..... Rochester
‡ Martin, Harold R. ..... Rochester
‡ Martin, John T. ..... Rochester
‡ Martin, Maurice J. ..... Rochester
*‡ Martin, William J. ..... Rochester
† Masserman, Richard L. ..... Rochester
† Masson, Duncan M. ..... Rochester
† Masson, James C. ..... Rochester
‡ Masson, James K. ..... Rochester
† Mathes, Peter B. ..... Rochester
‡ Mathieson, Don R. ..... Rochester
† Mathison, Robert D. ..... Rochester
Matson, Roland W. ..... Spring Valley
Mayne, John G. ..... Rochester
† Mayo, Charles H., II ..... White Bear Lake
‡ Merritt, Wallace A. ..... Rochester
† Mertens, Benny F. ..... Rochester
† Mess, Charles F. ..... Rochester
Meyer, William C. ..... Rochester
Midyett, F. Allan ..... Memphis, TN
† Miller, Joe I., Jr. ..... Rochester
‡ Miller, R. Drew ..... Rochester
‡ Miller, Ross H. ..... Rochester
† Miller, W. Eugene ..... Rochester
‡ Millikan, Clark H. ..... Rochester
‡ Mills, Stephen D. ..... Rochester
† Mitchell, John C. III ..... Rochester
† Moersch, Fred P. ..... Fort Lauderdale, FL
†‡ Moersch, Herman J. ..... Rochester
Moffitt, Emerson A. ..... Rochester
† Mokri, Bahram ..... Rochester
‡ Molnar, George D. ..... Rochester
† Montgomery, Hamilton ..... Rochester
† Moore, Barry B. ..... Rochester
‡ Moore, Gordon L., II ..... Rochester
Morgan, Stephan S. ..... Chesapeake, VA
Mori, Hideo ..... Grand Meadow
† Morimoto, Allen M. ..... Rochester
‡ Morlock, Carl G. ..... Rochester
‡ Morrow, George W., Jr. ..... Rochester
‡ Morse, Robert M. ..... Rochester
Muhm, John R. ..... Lawton, OK
† Mulcahy, John J. ..... Ann Arbor, MI
‡ Mulder, Donald W. ..... Rochester
‡ Muller, Sigfrid A. ..... Rochester
Mussey, Elizabeth ..... Rochester
‡ Myers, Thomas T. ..... Rochester
Nathan, Fred F. ..... Ellsworth, AFB, SD
† Nauman, James C. ..... Rochester
‡ Neault, Roger W. ..... Rochester
† Neel, H. Bryan, III ..... Rochester
† Nelson, Audrey M. ..... Rochester
Nesset, David G. ..... Rochester
† Nicholes, Karl R. K. ..... Rochester
† Nichols, Charles P. ..... Rochester
‡ Nichols, Donald R. ..... Rochester
† Niven, Robert G. ..... Rochester
‡ Nobrega, Fred T. ..... Rochester
† Nolan, Declan R. ..... Rochester
† Nuss, Donald ..... Rochester
‡ Obetz, Wendell ..... Rochester
Odyniec, Norman A. ..... Rochester
O'Duffy, John D. ..... Rochester
‡ Olsen, Arthur M. ..... Rochester
Olson, Grant E. ..... West Concord
‡ Olson, Neal R. ..... Rochester
‡ Onofrio, Burton M. ..... Rochester
† Onsgard, L. Kenneth ..... St. Petersburg, FL
† Opgrande, John D. ..... Rochester
‡ Opitz, Joachim L. ..... Rochester
‡ Osmundson, Philip J. ..... Rochester
‡ Owen, Charles A., Jr. ..... Rochester

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Zumbro Valley Medical Society *(Continued)*

† Oxman, Herbert A. ..... Rochester
† Pairolero, Peter C. ..... Rochester
‡ Palumbo, Pasquale J. ..... Rochester
† Paradis, Gaston R. ..... Rochester
† Pappalardo, Frank J. ..... Rochester
† Park, Moon Soo ..... Rochester
‡ Parker, Robert L. ..... Rochester
† Parkhill, Edith M. ..... Rochester
† Parry, Rodney R. ..... Rochester
Passmore, James A. ..... Ft. Sam Houston, TX
† Patrick, Donald L. ..... Rochester
† Pavlovsky, Miguel ..... Rochester
‡ Payne, W. Spencer ..... Rochester
† Pease, Gertrude L. ..... Rochester
‡ Perry, Harold O. ..... Rochester
Perry, Lawrence B. ..... Rochester
‡ Peters, Gustavus A. ..... Rochester
† Petersen, Magnus C. ..... Rochester
† Peterson, Charles A. ..... Rochester
‡ Peterson, Hamlet A. ..... Rochester
‡ Peterson, Lowell F. A. ..... Rochester
Petitt, Robert M. ..... Rochester
† Petty, Ray W. ..... Rochester
‡ Peyla, Thomas L. ..... Rochester
† Pien, Francis D. ..... Rochester
‡ Pierre, Robert V. ..... Rochester
† Pikler, George M. ..... Rochester
† Pliam, Michael B. ..... Rochester
† Plummer, Alan L. ..... Rochester
† Plummer, Leo J. ..... Rochester
‡ Pluth, James R. ..... Rochester
‡ Polley, Howard F. ..... Rochester
†‡ Pool, T. Lloyd ..... Rochester
† Port, Friedrich K. ..... Rochester
Poston, Lawrence M. ..... Caledonia
† Powell, David F. ..... Rochester
‡ Pozuelo-Utanda, Jose ..... Rochester
‡ Pratt, Joseph H., Jr. ..... Rochester
Prentice, James ..... Rochester
‡ Priestly, James T. ..... Rochester
† Pritchard, Douglas J. ..... Rochester
‡ Pruitt, Raymond D. ..... Rochester
‡ Pugh, David G. ..... Rochester
‡ Purnell, Don C. ..... Rochester
† Rahimi, Abbas ..... Rochester
† Raimundo, Hugo Sa ..... Rochester
‡ Ralston, Donald E. ..... Rochester
‡ Randall, Raymond ..... Rochester
† Reckles, Lawrence N. ..... Rochester
Reed, John H., Jr. ..... Minneapolis
‡ Reese, David F. ..... Rochester
Reeves, Bradford F. ..... Ft. Campbell, KY
† Reick, Robert R. ..... Rochester
Reilly, William F., Jr. ..... Davis-Gonthan AFB, AZ
† Reimer, Marvin S. ..... Rochester
‡ Reitemeier, Richard J. ..... Rochester
‡ ReMine, William H., Jr. ..... Rochester
‡ Restall, Charles J. ..... Rochester
Reynolds, James C. ..... San Antonio, TX
‡ Rhoton, Albert L., Jr. ..... Rochester
‡ Riggs, B. Lawrence ..... Rochester
Risser, Alden F. ..... Stewartville
‡ Ritter, Donald G. ..... Rochester
Rivan, Robert J. ..... Rochester
Rivers, Thomas A. ..... Colorado Springs, CO
‡ Robertson, Dennis M. ..... Rochester
† Robertson, Robert C. ..... Rochester
† Rodarte, Joe R. ..... Rochester
‡ Rome, Howard P. ..... Rochester
‡ Rooke, E. Douglas ..... Rochester
† Rosenbaum, Alan H. ..... Rochester
† Rosenbaum, Robert A. ..... Rochester
‡ Rosenow, Edward C., III ..... Rochester
Rosevear, John W. ..... Minneapolis
‡ Ross, James V., Jr. ..... Rochester
† Roubinian, Jirayr ..... Rochester
‡ Rovelstad, Randolph A. ..... Rochester
Roy, Paul H. J. ..... Quebec, Canada
†‡ Rucker, Charles W. ..... Rochester
† Rue, David S. ..... Rochester
‡ Rushton, Joseph G. ..... Rochester
† Russ, Homer H., Jr. ..... Rochester
† Russell, Rex D. ..... Rochester
† Ryan, William E. ..... Rochester
† Rydell, Ralph E. ..... Rochester
†‡ Rynearson, Edward H. ..... Rochester
† Salanga, Virgilio D. ..... Rochester
‡ Salassa, Robert M. ..... Rochester
‡ Sams, W. Mitchell, Jr. ..... Rochester
‡ Sander, Frank V., Jr. ..... Rochester
‡ Sanderson, David R. ..... Rochester
‡ Sandok, Burton A. ..... Rochester
† Sanfelippo, Peter M. ..... Rochester
† Satava, Richard M. ..... Rochester
Sauer, Robert L. ..... Preston
‡ Sauer, William G. ..... Rochester
‡ Sawtell, Robert R. ..... Rochester
Sayre, George P. ..... Rochester
† Scanlon, Edward S. ..... Rochester
‡ Scanlon, Paul W. ..... Rochester
‡ Schirger, Alexander ..... Rochester
† Schnur, Paul L. ..... Rochester
Schoen, Roland F., Jr. ..... San Francisco, CA
† Schoenberg, Bruce S. ..... Rochester
‡ Scholz, Donald A. ..... Rochester
Schrantz, Robert D. ..... Byron
† Schroeder, James R. ..... Rochester
Schutt, Allan J. ..... Rochester
Schutt, Ann H. ..... Rochester
† Schwab, Peter M. ..... Rochester
† Scotti, Angelo T. ..... Rochester
‡ Scudamore, Harold H. ..... Rochester
† Segal, Anthony ..... Rochester
† Segura, Joseph W. ..... Rochester
†‡ Seldon, T. Harry ..... Rochester
‡ Sessler, Alan D. ..... Rochester
† Seybold, Marjorie E. ..... Mooretown, NJ
† Shea, John H. ..... Rochester
† Shearin, Robert P. N. ..... Rochester
† Sheehan, William C. ..... Rochester
† Shen, Fu-hsuing ..... Rochester
‡ Sheps, Sheldon G. ..... Rochester
Shertzer, John H. ..... Ft. Bragg, NC
‡ Shick, Richard M. ..... Rochester
† Shih, Cheh S. ..... Rochester
‡ Siekert, Robert G. ..... Rochester
† Simmons, Paul B. ..... Rochester
Silverstein, Murray ..... Rochester
‡ Simons, John N. ..... Rochester
† Sippe, Joseph L. ..... Rochester
† Siqueira, Aristarco ..... Rochester
† Sisco, William T. ..... Rochester
† Sisemore, Daniel C. ..... Rochester
† Sizemore, Glen W. ..... Rochester
† Skaggs, Harold, Jr. ..... Rochester
Skaug, Harold M. ..... Chatfield
Skinner, Ira C., III ..... San Antonio, TX
‡ Slocumb, Charles H. ..... Rochester
† Smigiel, Mitchell R., Jr. ..... Rochester

Zumbro Valley Medical Society *(Continued)*

‡ Smith, Lucian A. ..... Rochester
† Smith, Ralph A., Jr. ..... Rochester
‡ Smith, Ralph E. ..... Rochester
Snyder, Robert E. ..... Spring Valley
† Soderstrom, Carl W., Jr. ..... Rochester
† Soltani, Jahanguir ..... Bayside, NY
Somerville, Gordon W. ..... Rochester
† Sondag, Glenn E. ..... Rochester
Sones, Donald A. ..... Rochester
‡ Soule, Edward H. ..... Rochester
† Speirs, Harvey R. ..... Rochester
‡ Spencer, Robert J. ..... Rochester
‡ Spiekerman, Ralph E. ..... Rochester
† Spil, Samuel ..... Rochester
‡ Spittell, John A., Jr. ..... Rochester
‡ Sprague, Randall G. ..... Rochester
Starkey, Thomas A. ..... St. Ord, GA
† Stauffer, Maurice H. ..... Rochester
Stecker, Raymond H. ..... APO New York, NY
† Steffee, William P. ..... Rochester
† Stein, Paul S. ..... Waukega, IL
† Steinfeld, Carroll M. ..... Rochester
‡ Steinhilber, Richard M. ..... Rochester
† Stenseth, Jon H. ..... Rochester
Stern, Barry L. ..... Phoenix, AZ
† Stevens, John C. ..... Rochester
† Stewart, John W. ..... Rochester
‡ Stickney, J. Minott ..... Rochester
‡ Stillwell, G. Keith ..... Rochester
†‡ Stilwell, George G. ..... Rochester
† Stine, Harold E. ..... Rochester
† Stonnington, Henry H. ..... Rochester
‡ Stroebel, Charles F., Jr. ..... Rochester
‡ Strong, Cameron G. ..... Rochester
† Su, Philo S. ..... Rochester
‡ Summerskill, William H. ..... Rochester
† Sun, Nora C. J. ..... Rochester
Sundt, Thoralf M., Jr. ..... Rochester
Sung, David T. W. ..... Rochester
† Suros, Juan ..... Rochester
‡ Svien, Hendrik J. ..... Rochester
† Svoboda, William B. ..... Rochester
Swanson, David W. ..... Rochester
† Switz, Donald M. ..... Rochester
† Tajik, Abdul J. ..... Rochester
† Takahashi, Raymond M. ..... Rochester
† Tangedahl, Tim N. ..... Rochester
† Tapia, Hugo R. ..... Rochester
‡ Taswell, Howard F. ..... Rochester
‡ Tauxe, Welby N. ..... Rochester
† Teem, Martin V., Jr. ..... Atlanta, GA
† Teunis, Bernard S. ..... Rochester
Thomas, Juergen E. ..... Rochester
† Thomas, William F., III ..... Rochester
† Thompson, Gershom J. ..... Rochester
‡ Thurber, Deloran L. ..... Rochester
† Tiede, James J. ..... Rochester
†‡ Tillisch, Jan H. ..... Rochester
† Tindel, Jerry R. ..... Rochester
‡ Tinkham, Robert G. ..... Rochester
Todd, David W. ..... APO New York, NY
Tompkins, Richard B. ..... Rochester
† Townsend, Gary L. ..... Rochester
‡ Trautmann, James C. ..... Rochester
† Tressler, Hubert A. ..... Rochester
Tsairis, Peter ..... Bethesda, MD
† Tschetter, Loren K. ..... Rochester
† Turner, Richard H. ..... Rochester
Tyce, Francis A. ..... Rochester
† Uihlein, Alfred ..... Rochester
‡ Underdahl, Laurentius O. ..... Rochester
‡ Utz, David C. ..... Rochester
Utz, Philip H. ..... La Crosse, WI
† Vanasek, Richard J. ..... Rochester
† van Boxel, John A. ..... Rochester
Van Dervoort, Robert L., Jr. ..... Carswell, AFB, TX
Van Herik, Martin ..... Rochester
† Van Ness, W. Noel T. ..... Ft. Jackson, SC
† Vargas-Cortes, Fernando ..... Rochester
‡ Vaughn, Louis D. ..... Rochester
Vermillion, Stanley E. ..... Goldsboro, NC
† Villanueva, Javier P. ..... Rochester
Virnig, Hildegard J. ..... Caledonia
† Vitas, Ovidio E. ..... Rochester
‡ Wagoner, Richard D. ..... Rochester
Wahner, Heinz W. ..... Rochester
†‡ Wakim, Khalil G. ..... Rochester
‡ Wallace, Robert B. ..... Rochester
Walls, Joseph T. ..... Lanstuhl, Germany
†‡ Walters, Waltman ..... Rochester
‡ Ward, L. Emmerson ..... Rochester
† Warren, Michael M. ..... Rochester
Watkins, Phillip C. ..... Birmingham, AL
† Watkins, Charles H. ..... Sun City, AZ
† Webel, Max L. ..... Rochester
Webster, Kirk H. ..... San Antonio, TX
‡ Weed, Lyle A. ..... Rochester
‡ Weeks, Richard E. ..... Rochester
† Wegener, Lee T. ..... Rochester
Weick, James K. ..... Camp Lejeune, NC
†‡ Weir, James F. ..... Rochester
† Welborn, William R., Jr. ..... Rochester
† Welch, John S. ..... Rochester
† Wellek, Mark A. ..... Rochester
‡ Wellman, William E. ..... Rochester
Wellner, Theodore O. ..... Rochester
† Welsch, John A. ..... Rochester
† Welsh, George F. ..... Rochester
‡ Wente, Harold A. ..... Rochester
† West, Thomas L. ..... Seattle, WA
Westbrook, Philip R. ..... Rochester
† Westmoreland, Barbara ..... Rochester
Westrup, John E. ..... Lanesboro
‡ Wharton, William P. ..... Rochester
‡ Whisnant, Jack P. ..... Rochester
† White, Roger D. ..... Rochester
‡ White, William L. ..... Rochester
Whittaker, Lorin D., Jr. ..... Fort Bragg, NC
Wiegand, Stewart E. ..... Atlanta, GA
‡ Wilkowske, Conrad J. ..... Rochester
† Williams, W. Byron ..... Rochester
† Williamson, Kenneth R. ..... Rochester
†‡ Willius, Fredrick A. ..... Rochester
† Wilmot, Thomas M. ..... Rochester
† Wilson, Charles S. ..... Rochester
Wilson, David M. ..... Rochester
‡ Wilson, Robert B. ..... Rochester
Wilson, Viktor O. ..... Minneapolis
‡ Wiltsie, John C. ..... Rochester
† Winders, Robert E. ..... Rochester
† Winegardner, G. E. ..... Rochester
‡ Winkelmann, Richard K. ..... Rochester
Witten, David M. ..... Aberdeen, WA
‡ Wollaeger, Eric E. ..... Rochester
† Wong, Freeman E. ..... Rochester
† Wong, Terry C. Y. ..... Rochester

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Zumbro Valley Medical Society *(Continued)*

‡ Wood, Lloyd T. ..... Rochester
‡ Woods, John E. ..... Rochester
† Woodward, Anthony H. ..... Rochester
‡ Woolner, Lewis B. ..... Rochester
‡ Worthington, John W., Jr. ..... Rochester
† Wurtele, Lester H. ..... Rochester
‡ Yoss, Robert E. ..... Rochester
† Youman, Joseph D., III ..... Rochester
‡ Young, H. Herman ..... Rochester
† Zack, John P. ..... Rochester
† Zeran, Theodore R. ..... Rochester
Zimmerman, Bruce R. ..... APO New York, NY
† Zujko, Richard D. ..... Rochester

ALPHABETIC ROSTER

Key to Symbols

* Deceased
\# Service
† Life, Associate, Affiliate and Resident
¶ Honorary

A

Aaro, Leonard A. ..... Rochester
† Abboud, Charles F. ..... Rochester
Abraham, Arden L. ..... Duluth
Abrams, Alexander, Jr. ..... St. Paul
Abrams, Donald J. ..... Shakopee
Abramson, Buron I. ..... Minneapolis
Abramson, Milton ..... Minneapolis
Abullarade, Jose A. ..... Minneapolis
Abuzzahab, Faruk S. ..... Minneapolis
Adair, Albert F., Jr. ..... St. Paul
Adams, Brandon L. W. ..... Minneapolis
Adams, Harold R. ..... St. Paul
Adams, Patrick J. ..... Shakopee
Adams, Richard I. ..... Minneapolis
Adcock, Leon L. ..... Minneapolis
Adicoff, Arnold ..... Minneapolis
Adkins, C. Douglas ..... Minneapolis
Adkins, James T. ..... Coon Rapids
† Adkins, William C. ..... Rochester
Adson, Martin A. ..... Rochester
Affeldt, Daniel E. ..... Kasson
Aga, John J. ..... Brainerd
Agustsson, Hreidar ..... Minneapolis
Ahern, Eugene E. ..... Minneapolis
† Ahlfs, Jacob J. ..... Avon
Ahlstrom, Robert C. ..... St. Paul
Ahmann, David L. ..... Rochester
Ahola, Kenneth E. ..... Hibbing
Ahrens, Curtis F. ..... Duluth
Ahrens, Robert M. ..... St. Paul
Akbar, Sajady ..... Minneapolis
Akhaven, Traz ..... Alexandria
Akins, Willard M. ..... Red Wing
Aksoy, Mustafa ..... St. Paul
Alari, Heino ..... Excelsior
Albrecht, Raymond J. ..... St. Paul
Alden, Charles W. ..... Kimball
Alden, John F. ..... St. Paul
Alexander, Harlan A. ..... Minneapolis
Alexander, Paul J. ..... Hibbing
† Aling, Charles A. ..... Minneapolis
Allen, James R. ..... Minneapolis
Allen, John H. ..... Montevideo
Allison, David D. ..... Litchfield
Alter, Milton ..... Minneapolis
Altman, Robert L. ..... St. Paul
*† Altnow, Hugo O. ..... Miami, FL
Alton, Donald G. ..... St. Paul
Amatuzio, Donald S. ..... Minneapolis
*† Amberg, Samuel ..... Rochester
Amerongen, Werner W. ..... St. Paul
Amra, Waleed ..... Chaska
Amren, Don P. ..... Minneapolis
Anderegg, Alfred F. ..... Minneapolis
† Andersen, Horace J. ..... Winona
Andersen, Howard A. ..... Rochester
Andersen, James G. ..... Minneapolis
Andersen, Robert C. ..... Minneapolis
Anderson, Arden O. ..... Brainerd
Anderson, Arnold S. ..... Minneapolis
Anderson, Carl F. ..... Rochester
Anderson, Chester A. ..... Hector
Anderson, Chester A. ..... Madison
Anderson, Dale L. ..... St. Paul
Anderson, David M. ..... Minneapolis
Anderson, David P., Jr. ..... Austin
Anderson, David W. ..... St. Paul
† Anderson, Ernest R. ..... Minneapolis
Anderson, Frank J. ..... Minneapolis
Anderson, Franklin C. ..... Owatonna
Anderson, Harold J. ..... Austin
† Anderson, James A. ..... Rochester
Anderson, James J. ..... St. Paul
Anderson, James M. ..... Duluth
Anderson, Jo E. ..... LeSueur
Anderson, John A. ..... Minneapolis
Anderson, John W. ..... Blue Earth
† Anderson, Karl W. ..... Excelsior
Anderson, Margaret C. ..... St. Paul
† Anderson, Mark J. ..... Sun City, AZ
Anderson, Markham J., Jr. ..... Rochester
† Anderson, Michael D. ..... Rochester
Anderson, Milton W. ..... Rochester
Anderson, Oscar D. ..... Mankato
Anderson, Quentin N. ..... Minneapolis
† Anderson, Richard D. ..... Rochester
† Anderson, Richard E. ..... Willmar
Anderson, Richard W. ..... St. Paul
Anderson, Richard W. ..... Minneapolis
Anderson, Roger E. ..... Minneapolis
Anderson, Roger L. ..... Minneapolis
Anderson, Russell H. ..... Virginia
Anderson, Thomas P. ..... Minneapolis
Anderson, U. Schuyler ..... Ft. Snelling
Anderson, W. Robert ..... Minneapolis
Anderson, Waldo P. ..... Buffalo
Anderson, Wallace E. ..... Minneapolis
Anderson, William H. ..... Minneapolis
Anderson, William T. ..... Minneapolis
Andre, James C. ..... Minneapolis
† Andreassen, Einar C. ..... Minneapolis
Andreassen, Rolf L. ..... Minneapolis
Andreini, Paul H. ..... Rochester
Andresen, Karl d'A ..... Minneapolis
Ankner, Frank J. ..... Minneapolis
Anonsen, Richard E. ..... Minneapolis
Anselment, Lois A. ..... Excelsior
Antolak, Stanley J., Jr. ..... St. Paul
Antonelli, Jordan J. ..... Hibbing
† Antonow, Arthur M. ..... Virginia
† Appelstein, Bruce ..... Rochester
† Arena, Paul J. ..... Rochester
† Arends, Archabald L. ..... Minneapolis
Arenson, Jeffrey A. ..... Minneapolis
Arey, Stuart Lane ..... Minneapolis
Arhelger, Stuart W. ..... Minneapolis
Arko, Frank R. ..... Hibbing
Arlander, Clarence E. ..... Minneapolis
Arlander, Thomas R. ..... Minneapolis
Arling, Leonard S. ..... Minneapolis
Armin, David W. ..... Two Harbors
Arms, James J. ..... Minneapolis
Armstrong, Byron H. ..... Minneapolis
Armstrong, Ralph S. ..... Winnebago

† Arndt, Harry W. ..... Detroit Lakes
Arnesen, John F. ..... Owatonna
Arnesen, Paul M. ..... Mankato
† Arnold, Ann W. ..... Minneapolis
Arnold, Thomas B. ..... Minneapolis
Arny, Frederick D. ..... St. Paul
† Arny, Frederick P. ..... St. Paul
† Aruguete, Alayne ..... Sandstone
† Aruguete, Jose ..... Sandstone
Ashby, Thomas M. ..... Decatur, GA
Ashmore, Herbert C. ..... St. Paul
Asp, Donald S. ..... Milaca
Asta, Joseph J. ..... Duluth
† Athens, Alvin G. ..... Santa Barbara, CA
Atmore, William G. ..... Duluth
Aufderheide, Arthur C. ..... Duluth
Aughenbaugh, John W. ..... Minneapolis
Aulick, Ernest J. ..... Paynesville
Auran, David B. ..... St. Paul
Aurelius, J. Richards ..... St. Paul
Ausman, Duane R. ..... St. Paul
† Aust, John C. ..... Morgantown, WV
Austrian, Sol ..... St. Paul
Autrey, William A. ..... St. Cloud
Avant, Robert F. ..... Minneapolis
Avren, Barbara L. ..... Virginia
Azad, Manouchehr M. ..... Minneapolis

B

Baab, Robert O. ..... Crookston
Baars, Conrad W. ..... Rochester
Babb, Frank S. ..... St. Paul
Bach, Jerome M. ..... Minneapolis
Backus, Byron C. ..... Cloquet
Backus, Lloyd B. ..... Minneapolis
Backus, Reno E. ..... Minneapolis
Backus, Reno W. ..... Cloquet
Bader, J. L. ..... Slayton
Baggenstoss, Archie H. ..... Rochester
Baggenstoss, Osmond J. ..... Minneapolis
Bagley, Charles M. ..... Duluth
Bagley, Elizabeth C. ..... Duluth
Bagley, Russell W. ..... Minneapolis
Bah, Merle C. ..... St. Paul
Baich, Velemir M. ..... Coleraine
† Bair, Hugo L. ..... Rochester
Baird, Raymond L. ..... Harmony
¶ Bajec, Dusan ..... Poljane, Yugoslavia
† Baken, Melvin P. ..... St. Paul
Baken, Melvin P., Jr. ..... Minneapolis
Baker, Abe B. ..... Minneapolis
Baker, C. Camak ..... Minneapolis
Baker, Chilton R., Jr. ..... St. Paul
Baker, Daniel R. ..... Anoka
† Baker, George S. ..... Rochester
† Baker, Harry R. ..... Hayfield
Baker, Hillier L., Jr. ..... Rochester
Baker, Jeannette L. ..... Fergus Falls
Baker, Lowell H. ..... Minneapolis
Baker, Milton E. ..... Minneapolis
Baker, Norman H. ..... Fergus Falls
Bakke, Arnold C. ..... Minneapolis
Bakkila, Henry E. ..... Duluth
Balce, Regino V. ..... St. Paul
Balderson, Robert P. ..... Grand Rapids
Balfour, William M. ..... Lawrence, KS
Balkin, Samuel G. ..... Minneapolis
Balkins, John W. ..... Minneapolis
Ballantine, Jerome J. ..... St. Cloud
Balmer, Albert I. ..... Duluth
Balogh, Charles J. ..... Minneapolis
Bancroft, Burton R., Jr. ..... St. Cloud
Bandt, Calvin M. ..... Minneapolis
Banfield, Frederick ..... Rochester
† Bank, Harry E. ..... Minneapolis
Banner, Edward A. ..... Rochester
Banovetz, John D. ..... Minneapolis
Baraga, Anthony R. ..... Hibbing
Baran, Ernest M. ..... Beaver Meadows, PA
Barbarisi, Charles F. ..... Mankato
Barbee, Charles W., Jr. ..... Ft. Stewart, GA
Barber, Tracy E. ..... Austin
Barnes, Richard E. ..... Aurora
Barnett, Arthur J. ..... St. Cloud
Barnett, Robert M. ..... Minneapolis
*† Barney, Leon A. ..... Duluth
Barno, Alex ..... Minneapolis
Barr, Lowell C. ..... Albert Lea
Barr, Lowell W. ..... Albert Lea
Barr, Maxwell M. ..... Minneapolis
* Barr, Robert N. ..... Minneapolis
Barrett, Patrick J. ..... Minneapolis
Barron, Jesse J. ..... Minneapolis
† Barron, Moses ..... Beverly Hills, CA
Barry, George J. ..... Minneapolis
Barry, Maurice J., Jr. ..... Rochester
Bart, Bruce J. ..... Minneapolis
Bartholdt, H. Peter ..... Cook
Bartholomew, Lloyd G. ..... Rochester
Bartness, John E. ..... Albert Lea
Bartzen, Peter J. ..... Duluth
Basinger, Harold P. ..... Windom
† Basinger, Homer P. ..... Windom
Bastron, James A. ..... Rochester
Batdorf, B. Niles ..... Mankato
Bateman, Clarence V. ..... Fergus Falls
Bauer, Eugene L. ..... St. Paul
Bauer, Paul G. ..... Faribault
Bauman, John C. ..... Foley
† Baumer, Robert J. ..... Rochester
Baumgartner, C. John ..... Minneapolis
Baumgartner, Florian H. ..... Albany
Bayrd, Edwin D. ..... Rochester
Beabout, John W. ..... Rochester
Beach, Northrop ..... Minneapolis
Beahrs, Oliver H. ..... Rochester
Bealka, Neil M. ..... Stillwater
Bean, Charles N. ..... Waconia
† Bean, William J. ..... Rochester
Beard, Archibald H., Jr. ..... Minneapolis
Beaton, J. Gordon ..... Northfield
Bechamps, Gerald J. ..... Fort Eustis, VA
Beck, Charles J. ..... No. St. Paul
† Beckenbaugh, Robert D. ..... Rochester
Becker, Frederic T. ..... Duluth
† Becker, Paul W. ..... Rochester
Beckering, Gerrit ..... Edgerton
Beckering, Roland G. ..... Edgerton
† Beckley, James M. ..... Rochester

Becklund, Robert W. ..... Minneapolis
Beckman, Donovan L. ..... St. Paul
† Beeckler, Donald C. ..... Rochester
Beek, Harvey O. ..... St. Paul
Beeman, John A. ..... Minneapolis
Beer, John J. ..... St. Paul
Behr, Orlo K. ..... Crookston
Beirstein, Samuel ..... Minneapolis
Beiswanger, Richard H. ..... Minneapolis
Belau, Paul G. ..... Rochester
Belcher, Royden A. ..... Little Falls
Bell, Donald C. ..... Minneapolis
Bell, Harry M., Jr. ..... Duluth
Bellomo, James ..... St. Paul
Bellomo, John ..... Fairmont
Bellville, Titus P. ..... Minneapolis
Belshe, Joseph ..... St. Cloud
Belsito, Alphonso A. ..... St. Paul
Belz, Reinmar ..... St. Paul
Bendel, Richard P. ..... Minneapolis
Bendel, William L., Jr. ..... Minneapolis
Bender, James H. ..... Brainerd
Bendix, Lester H. ..... Annandale
† Benell, Otto E. ..... Britt
Benesh, Louis A. ..... Minneapolis
Benjamin, Charles I. ..... Glenwood
Benjamin, Edwin G. ..... Minneapolis
Benjamin, Harold G. ..... Minneapolis
Benjamin, Richard D. ..... Minneapolis
Benjamin, Robert B. ..... Minneapolis
Benjamin, Roger J. ..... Owatonna
† Banjamin, Walter G. ..... Pipestone
Bennett, Clayton J. ..... Rochester
Bensman, Alan S. ..... Minneapolis
† Benson, Ralph C., Jr. ..... Rochester
Benthack, Elaine M. ..... Minneapolis
Bentz, Herman D. ..... Anoka
Bentzin, C. K. ..... Monticello
Berestka, Stephen J. ..... Minneapolis
Berg, Arnold M. ..... Thief River Falls
Berg, Clinton C. ..... Excelsior
Berg, John H. ..... Montgomery
† Bergan, Otto ..... Clinton
Bergan, Robert O. ..... Duluth
Berge, Harry L. ..... Mora
Berge, Kenneth G. ..... Rochester
Berger Alex G. ..... Minneapolis
Berger, Phil R. ..... St. Cloud
Bergersen, Dean H. ..... Arlington
Bergh, Allen V. ..... St. Paul
Bergh, George S. ..... Minneapolis
Bergh, Solveig M. ..... Minneapolis
Berglund, Alvin E. ..... Cambridge
Berglund, Eldon B. ..... Minneapolis
Bergquist, James R. ..... Minneapolis
Bergstrom, Ralph W., Jr. ..... Maple Plain
† Bergstrom, William J. ..... Minneapolis
† Berkman, John M. ..... Rochester
Berkwitz, Nathaniel J. ..... Minneapolis
Berman, David A. ..... Minneapolis
Berman, Reuben ..... Minneapolis
† Berman, Stanley Z. ..... Rochester
Berner, Herbert W., Jr. ..... Worthington
Bernier, Merrill J. ..... No. St. Paul
Berns, Max H. ..... Duluth
Bernstein, Dorothy M. ..... Minneapolis
Bernstein, Irving C. ..... Minneapolis
† Bernstein, Sidney S. ..... Rochester
† Bernstein, William C. ..... St. Paul
Berris, Harold ..... Minneapolis
Berry, Ronald N. ..... Minneapolis
Berzins, Rainis ..... Minneapolis
† Bessesen, Alfred N. ..... Minneapolis
† Besson, Augustin ..... Rochester
Beuning, John B. ..... St. Cloud
Beuret, Lawrence J. ..... Rockford, IL
Bevis, William D. ..... Minneapolis
† Beyerlein, Charles R. ..... Rochester
Bhattacharyya, Sisir K. ..... Battle Lake
† Bianco, Anthony J. ..... Vero Beach, FL
Bianco, Anthony J., Jr. ..... Rochester
Bickel, William H. ..... Rochester
Bieger, R. Cyril ..... Minneapolis
Biery, M. Barbara ..... Minneapolis
† Bieter, Raymond N. ..... Minneapolis
Bieter, Thomas G. ..... St. Paul
Bigler, Earl E. ..... Perham
Bigler, Ivan E. ..... Perham
Bilgutay, Aydin M. ..... Minneapolis
Bilka, Paul J. ..... Minneapolis
Billings, Harry H. ..... Red Wing
Billman, Herbert R. ..... Minneapolis
Biltz, John F. ..... Red Wing
Binder, Manuel R. ..... Minneapolis
Birkebak, Roland C. ..... St. Paul
† Birkemeyer, Eugene J. ..... Rochester
Birkey, Thomas G. ..... Montevideo
Bisel, Harry F. ..... Rochester
Bissinger, Lester L. ..... Brainerd
Bittick, Wilbur H. ..... Minneapolis
Bjornson, Robert G. B. ..... St. Paul
Black, B. Marden ..... Rochester
† Black, Earl J. ..... St. Paul
Black, Leo F. ..... Rochester
Black, William A. ..... New Ulm
Blackard, Clyde E. ..... Minneapolis
Blackburn, Henry W., Jr. ..... St. Paul
Blake, Allan J. ..... Hopkins
Blake, James A. ..... Hopkins
Blake, Paul S. ..... Minneapolis
† Blanco-Benavides, Roberto ..... Rochester
Bloch, Henry S. ..... Minneapolis
Blocdel, Traugott J. ..... Osseo
Blomberg, Robert D. ..... Minneapolis
Blomberg, William R. ..... St. Paul
Bloom, David ..... Minneapolis
† Bloom, Joseph ..... Pompano Beach, FL
Bloom, Norman B. ..... Minneapolis
Blum, Clifford J. ..... Duluth
Blumberg, Henry B. ..... St. Paul
† Blume, Warren T. ..... Rochester
Blumenthal, Malcolm N. ..... Minneapolis
Blumer, Arlo R. ..... Albert Lea
Boardman, Dalmon V. ..... Winona
Boardman, Peter J. ..... Wayzata
Boardman, William J. ..... Minneapolis
† Bock, Rolland A. ..... St. Paul
Boecker, Bernhard ..... Duluth
Bofenkamp, Benjamin ..... Minneapolis
† Bofenkamp, Ferdinand W. ..... Luverne
*† Bohn, Donald G. ..... Minneapolis
† Boies, Lawrence R. ..... Hopkins
Boies, Lawrence R., Jr. ..... St. Paul
Boline, Clifford A. ..... Battle Lake
Bologna, Camillo V. ..... Moorhead
Bolt, Donald A. ..... Minneapolis
Bolz, J. Arnold ..... Grand Rapids

† Boman, Paul G. ..... Duluth
Boman, Peter L. ..... Duluth
* Bonebrake, Robert A. ..... Gurnee, IL
Bonewell, George W. ..... Minneapolis
Bonello, Frank J. ..... St. Paul
† Bonfil-Roberts, Enrique A. ..... Rochester
Bonner, John L. ..... Grand Rapids
Boody, George ..... Cambridge
Boone, Ervin S. ..... Luverne
Borgerson, Arthur H. ..... Long Prairie
Borgerson, M. A. ..... Hanley Falls
Borman, Chauncey N. ..... Minneapolis
Borowicz, Leonard A. ..... Minneapolis
Bosland, Howard G. ..... Rochester
Bosley, Patrick ..... Balaton
† Bottolfson, B. T. ..... Moorhead
† Bouma, Lewis R. ..... St. Paul
Bouquet, Bertram J. ..... Wabasha
Bouthilet, Florence J. ..... Minneapolis
† Bowers, Gordon G. ..... Excelsior
Bowers, Robert N. ..... Lake City
Bowlin, Paul F. ..... Minneapolis
Boyd, David A., Jr. ..... Rochester
Boyd, Frank E. ..... Pipestone
† Boyer, Andrew G. ..... Rochester
Boyer, Samuel H. ..... Duluth
Boyle, Francis J. ..... Springfield
† Boynton, Ruth E. ..... Miami, FL
† Boysen, Herbert ..... Madelia
† Boyum, Allan J. ..... Minneapolis
Bozanich, Milosh S. ..... St. Cloud
† Braasch, William F. ..... Rochester
† Barbec, Paul F. ..... Hastings
Brace, Ray J. ..... Clinton
Bradford, David S. ..... Minneapolis
Bradley, Jeanne B. ..... Minneapolis
Bradley, John G. ..... Minneapolis
Bradley, William E. ..... Minneapolis
Brady, Charles H., Jr. ..... Mankato
Brainerd, John B. ..... St. Paul
† Brand, William A. ..... Redwood Falls
Brandenburg Robert O. ..... Rochester
Brandt, Henry E. ..... Minneapolis
Bransford, Paul W. ..... Minneapolis
Bratholdt, James W. ..... Watertown
† Bratrud, Edward ..... Alexandria
*† Bratrude, Earl J. ..... Hopkins
Brattensborg, Henry J. ..... St. Cloud
Brauer, William W. ..... Minneapolis
Braun, Ohrmundt C. ..... Grand Rapids
Braun, Rene ..... Minneapolis
Bray, Jerome L. ..... Thief River Falls
Bray, Philip N. ..... Duluth
Breen, John J. ..... St. Paul
Breitenbucher, Robert B. ..... Minneapolis
† Breivis, James S. ..... Rochester
† Brekke, Harvey J. ..... Minneapolis
† Brende, Joel O. ..... Topeka, KS
Brenk, Paul E. ..... Detroit Lakes
Brennan, Joseph G. ..... Minneapolis
Brettingen, Larry J. ..... Mora
Bretzke, Carl O. ..... Hutchinson
Brewster, Robert C. ..... Grand Forks, ND
Briggs, John F. ..... St. Paul
Briggs, Thomas G. ..... White Bear Lake
Brigham, Charles F., Jr. ..... St. Cloud
Brill, Alice K. ..... Minneapolis
Brink, Adlai A. ..... Baudette
Brink, Donald M. ..... St. Peter
† Brinkman, James F. ..... Rochester
Briones, Bienvenido R. ..... Hopkins
Broadhurst, Kennon E. ..... Detroit Lakes
Broadie, Thomas E. ..... St. Paul
† Brockberg, Daryl G. ..... St. Paul
† Brockberg, James A. ..... St. Paul
Brodhun, John C. ..... Rochester
† Brodie, Walter D. ..... St. Paul
Broker, Henry M. ..... St. Cloud
Broman, Harold R., Jr. ..... No. St. Paul
Bromer, Michael D. ..... Minneapolis
Brooker, Warren J. ..... Duluth
† Brooks, Charles N. ..... Wayzata
† Brown, Alan P. ..... Rochester
† Brown, Alex E. ..... Brandenton, FL
Brown, Arnold L. ..... Rochester
Brown, Charles T. ..... St. Paul
Brown, Christopher J. ..... St. Paul
Brown, Cyrus C., Jr. ..... Duluth
Brown, Frank T. ..... St. Cloud
Brown, Glenn W. ..... Halstad
Brown, Hector M. ..... St. Paul
Brown, Henry A. ..... Rochester
Brown, James E., Jr. ..... St. Paul
Brown, James P. ..... St. Paul
Brown, Joe R. ..... Rochester
Brown, John H. ..... Minneapolis
Brown, John M. ..... St. Paul
† Brown, Philip W. ..... Rochester
Brown, Philip W., Jr. ..... Rochester
Brown, Russell T. ..... Browerville
† Brown, Stephen R. ..... Rochester
Brown, William D., Jr. ..... Minneapolis
Brownfield, James A. ..... Minneapolis
Brubaker, Richard F. ..... Rochester
Bruhl, Heinz H. ..... Faribault
Bruhl, Martin G. ..... St. Paul
† Brusegard, James F. ..... Red Wing
† Bryan, James W. ..... Rochester
Bryan, Richard S. ..... Rochester
Bucher, Foster D. ..... Starbuck
Buchstein, Harold F. ..... Minneapolis
† Buck, Frederick H. ..... Shakopee
† Buckley, John P. ..... Rochester
Buckley, Joseph J. ..... Minneapolis
Buckley, Robert P. ..... Duluth
Buege, William ..... Albert Lea
Buentipo, Benigno ..... Mora
Buesgens, Ralph H. ..... Waterville
Bugby, Robert D. ..... Minneapolis
Bugenstein, Robert H. ..... Minneapolis
† Buie, Louis A. ..... Rochester
Buie, Louis A., Jr. ..... Minneapolis
Bulinski, Theodore J. ..... St. Paul
Bulluck, Matthew H. ..... Duluth
† Bunch, Thomas W. ..... Rochester
Bundt, Robert E. ..... Minneapolis
Bunker, Bevan W. ..... Anoka
† Buntain, William L. ..... Rochester
Buran, David J. ..... Minneapolis
Burchell, Howard B. ..... Minneapolis
Buresh, Kenneth L. ..... Owatonna
Burgert, E. O., Jr. ..... Rochester
† Burgess, John N. ..... Rochester
Burich, Harry F. ..... Rochester
Burke, Edmund C. ..... Rochester
Burkholder, Dayton D. ..... Anoka
Burklund, Edwin C. ..... St. Paul
Burlingame, David A. ..... St. Paul

Burman, Richard E. ..... Aitkin
Burmeister, Richard O. ..... St. Paul
Burnett, Joseph W. ..... New Ulm
Burnham, Wesley H. ..... Minneapolis
† Burns, Catherine ..... Excelsior
† Burns, Jess R. ..... Rochester
Burns, John M. ..... St. Paul
† Burns, M. A. ..... Edina
Burseth, Edgar C. ..... Mora
Burton, J. Richard ..... St. Paul
Burton, Thomas P. ..... Minneapolis
† Bush, David J. ..... Rochester
Bush, Robert P. ..... St. Paul
Butler, John K. ..... Cloquet
Butt, Hugh R. ..... Rochester
Butwinick, Conrad S. ..... St. Paul
† Butzer, John A. ..... Mankato
† Buza, Robert C. ..... Rochester
† Buzanowski, Krystyna ..... Rochester
† Byer, David E. ..... Rochester
Byrne, William J. ..... St. Paul

C

† Cabanela, Miguel E. ..... Rochester
Cable, Morris L. ..... Minneapolis
† Cabot, Clyde M. ..... Deerfield, FL
Cadbury, Jane B. ..... Mankato
Cain, Clark L. ..... St. Paul
Cain, James C. ..... Rochester
Cain, James H. ..... Alexandria
Cairns, Robert J. ..... Redwood Falls
*† Calhoun, Frank W. ..... Albert Lea
Calin, S. Hartley ..... Minneapolis
Callahan, John A. ..... Rochester
† Camacho, Luis-Guillermo ..... Rochester
Cameron, Alan J. ..... Rochester
Cameron, Bruce P. ..... Minneapolis
† Cameron, Isabell L. ..... Minneapolis
Cameron, John H. ..... Clovis, NM
Camp, Ray J. ..... Madison
† Campa, Herman K. ..... Rochester
Campaigne, Robert J. ..... Duluth
Campbell, Denis V. ..... Minneapolis
Campbell, Donald C. ..... Rochester
Campbell, John C. ..... Albert Lea
† Campbell, John T. ..... Rochester
Campbell, Malcom K. ..... Rochester
Campbell, Marilyn R. M. ..... Minneapolis
Campbell, Orwood J. ..... Minneapolis
† Campbell, Ronald G. ..... Minneapolis
Campos, Amador C. ..... Aurora
Cangemi, Francis E. ..... Rochester
Canine, James L. ..... So. St. Paul
† Cannon, Patrick J. ..... Rochester
Cant, Wilbur F. ..... Red Wing
*† Cantwell, William F. ..... International Falls
Card, William H. ..... Minneapolis
† Carder, George A. ..... Rochester
Cardle, George E. ..... Brainerd
Cardle, James G. ..... Minneapolis
Cardle, John B. ..... Minneapolis
Carey, Lewis S. ..... St. Paul
Carlander, Lester W. ..... Minneapolis
Carley, Richard B. ..... St. Paul
Carlon, Donald L. ..... Moorhead
Carlson, Carl E. ..... Alexandria
Carlson, Charles V. ..... Mound
Carlson, David J. ..... Minneapolis
Carlson, Harley C. ..... Rochester
Carlson, Homer J. ..... Pelican Rapids
Carlson, John V. ..... Westbrook
Carlson, Lawrence ..... Minneapolis
Carlson, Lloyd E. ..... Worthington
Carlson, Vernon J. ..... Moorhead
Carnahan, Charles E. ..... Grandview, MO
Carney, Francoise ..... Rochester
Carr, David T. ..... Rochester
Carr, William J. ..... Minneapolis
Carrier, Thomas C. ..... Minneapolis
Carryer, Haddon M. ..... Rochester
Carter, Earl T. ..... Rochester
Carter, Kenneth R. ..... Granite Falls
Carter, Robert E. ..... Duluth
Carter, Robert G. ..... Minneapolis
Carthey, Frank J. ..... New Ulm
Caspers, Carl G. ..... Minneapolis
Cass, Alexander S. ..... St. Paul
† Cassan, Stanley A. ..... Rochester
Castle, Donald D. ..... St. Paul
Catlin, Theodore J. ..... Buffalo
Cauble, Charles F. ..... Minneapolis
† Cavanor, Frank T. ..... Minneapolis
Cavert, H. Mead ..... Minneapolis
Cedarleaf, Cherry B. ..... White Bear Lake
Ceder, Elmer T. ..... Minneapolis
Cella, Joseph A. ..... Minneapolis
† Ceplecha, Stanley F. ..... Redwood Falls
Cervenka, Charles F. ..... New Prague
Cesnik, Robert J. ..... Sauk Rapids
Chadbourn, Wayne A. ..... Minneapolis
Chalgren, William S. ..... Mankato
Challman, S. Alan ..... Minneapolis
Chandler, William M. ..... Minneapolis
† Chatterton, Carl C. ..... St. Paul
Chedister, Charles R. ..... Minneapolis
† Cheng, Vincent S. T. ..... Rochester
Chermak, Francis G. ..... Phoenix, AZ
Chervenak, William A. ..... Marine-on-St. Croix
† Chesebro, James H. ..... Rochester
Chesler, Merrill D. ..... Minneapolis
† Chidlow, Judd H. ..... Rochester
Child, Sherman B. ..... Minneapolis
Childs, Donald S., Jr. ..... Rochester
† Chilgren, Keith V. ..... Minneapolis
† Ching, Ernesto ..... Rochester
Chisholm, Tague C. ..... Minneapolis
Chou, Shelley N. ..... Minneapolis
Christensen, Clarence H. ..... Duluth
† Christensen, Eli E. ..... Winona
Christensen, Llewellyn E. ..... Minneapolis
Christensen, Norman A. ..... Rochester
† Christenson, Carl E. ..... New Brighton
Christenson, Leland R. ..... Maple Plain
Christgau, Roger A. ..... Minneapolis
Christian, William L. ..... Minneapolis
Christiansen, Harold A. ..... Jackson
Chumbley, Lee C. ..... Patuxent River, MD
Chunn, Stanley S. ..... Willmar

Church, Gerald E. ..... Two Harbors
† Chychota, Norman N. ..... Rochester
† Cich, John A. ..... West St. Paul
Ciriacy, Edward W. ..... Minneapolis
Clagett, O. Theron ..... Rochester
Clapp, Hubert D. ..... Crookston
† Clark, Edward C. ..... San Francisco, CA
Clark, Elizabeth A. (Mrs. Halbert) ..... Duluth
† Clark, Harry B. ..... St. Cloud
Clark, Ivan T. ..... Sun City, AZ
† Clark, Leslie W. ..... Manchester, IA
Clark, Malcolm D. ..... Minneapolis
Clark, Robert S. ..... Minneapolis
Clark, W. Bruce ..... St. Paul
Clarke, Dean T. ..... Faribault
Clarke, John W. ..... Waconia
Clay, Lyman B. ..... Minneapolis
Cleary, John ..... St. Paul
Clifford, Thomas M. ..... Silver Bay
† Clifton, Theodore A. ..... Hollywood, FL
Cline, David W. ..... Minneapolis
† Cloherty, Martin G. ..... Rochester
Close, Gerald A. ..... Glencoe
Closuit, Frederick ..... Aitkin
Cochrane, Byron B. ..... St. Paul
Cochrane, Ray F. ..... Minneapolis
Coddon, Walter D. ..... St. Paul
Code, Charles F. ..... Rochester
Coder, Donald M. ..... Jacksonville, FL
Cody, D. Thane ..... Rochester
† Cody, Michael C. ..... Rochester
Coe, John I. ..... Minneapolis
Coe, Robert O. ..... Virginia
Cohan, Richard C. ..... Minneapolis
Cohen, Bernard A. ..... Minneapolis
Cohen, Ephraim B. ..... Minneapolis
Cohen, Henry W. ..... Wayzata
† Cohen, Manley ..... Long Beach, CA
Cohen, Sumner S. ..... Minneapolis
Colago, Victor M. ..... Browns Valley
Colby, Malcolm Y., Jr. ..... Rochester
† Colby, Woodard L. ..... St. Paul
Cole, George A. ..... Albert Lea
Cole, James S. ..... Minneapolis
Cole, Wallace H. ..... St. Paul
Coleman, John B. ..... St. Paul
† Coleman, Robert L. ..... Rochester
Coleman, Thomas P. ..... Addis Abeba, Ethiopia
Coles, Douglas T. ..... Rochester
Coll, James J. ..... Duluth
† Collins, Arthur N. ..... Duluth
Collins, Roger T. ..... Duluth
Colliton, Patrick A. ..... Moorhead
Colman, Edward L. ..... Fergus Falls
Colton, Roger S. ..... St. Paul
† Colville, David ..... Rochester
Comfort, Thomas H. ..... St. Paul
Conley, Francis W. ..... Duluth
Conley, Robert H. ..... Mankato
Conlin, F. Dixon ..... Minneapolis
Conlon, Daniel C. ..... Minneapolis
Conn, Richard L. ..... Albuquerque, NM
Connolly, Coleman J. ..... St. Paul
Connolly, Daniel C. ..... Rochester
Connolly, Joseph P. ..... So. St. Paul
† Connor, Ann C. S. ..... Rochester
† Connor, Charles E. ..... St. Paul
† Connor, David G. ..... Minneapolis
† Cook, Edward N. ..... Rochester
Coombs, Carl H. ..... Cass Lake
Cooper, Charles C. ..... Moose Lake
† Cooper, Herbert A. ..... Rochester
Cooper, Jack M. ..... St. Paul
Cooper, John P. ..... Minneapolis
Cooper, Robert R. ..... Minneapolis
Cooper, Talbert ..... Rochester
† Cooperman, Avram M. ..... Rochester
Cope, Hershel B. ..... Virginia
Corbin, Kendall B. ..... Rochester
† Corniea, Albert D. ..... Minneapolis
† Corrado, Angelini ..... Rochester
Correa, Dale H. ..... Minneapolis
Corrigan, Cyril J. ..... Rochester
Corson, Wilfred A. ..... Minneapolis
Cortez, Daniel P. ..... Minneapolis
Cosgriff, James A., Jr. ..... Olivia
Cotton, Gerald E. ..... Duluth
Coulter, Harold E. ..... Minneapolis
† Countryman, Roger S. ..... Saratoga, CA
Courteau, Robert D. ..... Los Angeles, CA
Coventry, Markham B. ..... Rochester
Coventry, William D. ..... Duluth
Covey, Kenneth W. ..... Moorhead
Cowan, Donald W. ..... Minneapolis
Cowan, Gary A. ..... Duluth
Cowan, George M. ..... Duluth
Cox, Russell L. ..... Estherville, IA
Coy, Douglas J. ..... Grand Rapids
Craig, David M. ..... St. Paul
Craig, M. Elizabeth ..... Minneapolis
Cram, Barclay M. ..... St. Paul
Cramer, Glen G. ..... New Brighton
† Cranmer, Richard R. ..... Laguna Hills, CA
Cranston, Robert W. ..... Minneapolis
Creevy, Charles D. ..... Minneapolis
Creps, James R. ..... Duluth
Cress, Thomas L. ..... St. Cloud
Crislip, George D. ..... Waconia
Cronwell, Bernhard J. ..... Austin
Crossley, Kent B. ..... Minneapolis
Crow, Earl R. ..... Minnetonka
Crow, George M. ..... International Falls
† Crowder, David F. ..... Rochester
Crowley, James H. ..... St. Paul
Crowley, Leonard V. ..... Minneapolis
Crudo, Vincent D. ..... St. Paul
Crum, Arthur Z. ..... St. Paul
Crutchfield, Charles E. ..... St. Paul
Crutchfield, Susan E. ..... St. Paul
Cullado, Andrionico F. ..... Mineapolis
† Cullen, Joseph M. ..... Rochester
Cullen, Robert M. ..... So. Africa
Culligan, David E. ..... St. Paul
Culligan, John A. ..... St. Paul
Culligan, Leo C. ..... Minneapolis
Culp, Clyde E. ..... Rochester
Culp, Ormond S. ..... Rochester
Culver, Lucian G. ..... St. Paul
Cumming, Edward D. ..... St. Paul
Cumming, Robert J. ..... St. Cloud
Cundy, Donald T. ..... Minneapolis
Cupps, Roger E. ..... Rochester
Curran, John P. ..... Minneapolis
Cushing, Richard T. ..... Minneapolis
† Cutts, George ..... Minneapolis

D

Daehlin, Rolf ..... Fergus Falls
Dagg, Earl ..... Thief River Falls
Daggett, Donald R. ..... Minneapolis
*† Dahl, Elmer O. ..... Minneapolis
Dahl, James C. ..... Minneapolis
† Dahl, John A. ..... Minneapolis
Dahlin, David C. ..... Rochester
Dahlstrom, Donald D. ..... Minneapolis
Dale, Allan J. D. ..... Rochester
Dale, Les N. ..... Hastings
Daly, Alfred E. ..... St. Paul
Damberg, Sheldon W. ..... St. Paul
† Daniel, Donald H. ..... Minneapolis
† Daniel, William W. ..... Rochester
Danielson, Lennox ..... Litchfield
Danyluk, Michael ..... Minneapolis
Dargay, Cyril P. ..... Rochester
† Datnow, Boris ..... Rochester
Daugherty, Guy W. ..... Rochester
Daumann, Roy F. ..... Minneapolis
Dauphine, Richard T. ..... FPO, NY, NY
David, Reuben ..... Hopkins
Davidson, A. Dale ..... Duluth
Davidson, J. Duane ..... Thief River Falls
† Davis, Austin C. ..... Pompano Beach, FL
† Davis, David L. ..... Rochester
Davis, Edward V. ..... St. Paul
Davis, Eunice A. ..... St. Paul
Davis, George D. ..... Rochester
† Davis, Lloyd T. ..... Wadena
Davis, Luther F. ..... Wadena
Davis, Michael W. ..... Minneapolis
Davis, Raymond D. ..... Stockton, CA
Davis, Thomas H. ..... Minneapolis
Davis, William I. ..... Moose Lake
† Davis, Zev ..... Rochester
Dawson, Lorin D. ..... Worthington
Dawson, W. John, Jr. ..... Minneapolis
Dearing, William H. ..... Rochester
Deason, Keith B. ..... Chisago City
* Decker, Charles H. ..... St. Paul
Decker, Charles W. ..... Hibbing
Decker, David G. ..... Rochester
† Dedeker, Kenneth L. ..... Minneapolis
† Deffner, Norman F. ..... Rochester
Degallier, Daniel ..... Winona
Deger, Grant E. ..... Fairchild, AFB, WA
Delahunty, John R. ..... Red Wing
deLeon, Buenaventura ..... Stillwater
Delmore, John L. ..... Roseau
Delzell, Allen W. ..... Minneapolis
De Marais, Lloyd C. ..... Hibbing
Demo, Robert A. ..... Albert Lea
Derauf, Donald E. ..... St. Paul
Derechin, William ..... St. Paul
DeRemee, Richard A. ..... Rochester
Desai, B. J. ..... Worthington
† de Souza e Silva, Nelson A. ..... Rochester
De Santo, Lawrence W. ..... Rochester
† Detenbeck, Lee C. ..... Rochester
Deters, Donald C. ..... St. Paul
Deutsch, Robert J. ..... Duluth
Devine, Kenneth D. ..... Rochester
Devloo, Robert A. ..... Rochester
DeWeerd, James H. ..... Rochester
Deweese, Joel T. ..... Bemidji
Deweese, Wilford J. ..... Bemidji
deWerd, Robert W. ..... Owatonna
Dewey, Donald H. ..... Owatonna
Diamond, Robert A. ..... Minneapolis
Dickinson, Paul B. ..... St. Paul
Dickman, Roy W. ..... Minneapolis
Dickson, Franklin H. ..... Proctor
Didier, Edward P. ..... Rochester
Diefenbach, Eugene J. ..... Minneapolis
Diego, Benito B. ..... Fridley
† Diehl, Harold S. ..... New York, NY
Diehl, James J. ..... Minneapolis
Dieperink, Willem ..... St. Paul
Dierker, Heinrich A. ..... Minneapolis
Diessner, Ardell W. ..... Stillwater
Diessner, Grant R. ..... Rochester
† Diessner, Henry D. ..... Hopkins
Dillie, Donald E. ..... Litchfield
Dillenburg, Cyril J. ..... Crookston
Dimants, Janis, Jr. ..... Minneapolis
† DiPasquale, Joseph A. ..... Rochester
† Disney, Thomas F. ..... Rochester, NY
† Dittrich, Raymond ..... St. Paul
† Djalilian, Mohsen ..... Rochester
Doan, Robert E. ..... Wayzata
† Dobes, William L., Jr. ..... Rochester
Dobbs, Richard L. ..... Duluth
Dobler, Manfred G. ..... Ely
† Dobmeier, Lawrence J. ..... Rochester
† Dobrin, Dale T. ..... Minneapolis
Dobson, Mervin W. ..... Mankato
Dobyns, James H. ..... Rochester
Docherty, John A. ..... Edina
Dockerty, Malcolm B. ..... Rochester
Docksey, John W. ..... Willmar
Dodds, William C. ..... Detroit Lakes
Doebler, Myron I. ..... Mora
Doherty, Elmer M. ..... New Prague
Dokken, James H. ..... Windom
Doman, Victor W. ..... Lakefield
Doms, Vernon A. ..... Elbow Lake
† Donaldson, Charles S. ..... St. Cloud
Donatelle, Edward P. ..... Minneapolis
† Donoghue, Edmund R., Jr. ..... Rochester
Donoghue, Francis E. ..... Rochester
Donovan, Daniel L. ..... New Brighton
Dooley, Robert T. ..... St. Paul
† Dorge, Richard I. ..... Minneapolis
Dornbach, Robert A. ..... Minneapolis
Dorsey, George C., Jr. ..... Minneapolis
Dorsey, William E. ..... Minneapolis
Doscherholmen, Alfred ..... Minneapolis
Dougan, Jerome W. ..... Minneapolis
Douglass, Bruce E. ..... Rochester
Douglass, Jesse E. ..... Canon Falls
do Vale, Joao M. ..... Minneapolis
† Downey, Gale T. ..... Rochester
† Doxey, Gilbert L. ..... Minneapolis
Doyle, James R. ..... Rochester
† Dozois, Roger R. ..... Rochester
† Dredge, Thomas E. ..... Minneapolis
† Dredge, Thomas E., Jr. ..... Minneapolis
Drexler, Charles J. ..... Duluth
Drexler, George W. ..... Blue Earth
Dreyling, Roger A. ..... Eden Valley
Drill, Frederick E. ..... Minneapolis
Drill, Herman E. ..... Hopkins

† Drips, Della G. ..... Rochester
† Driscoll, Thomas P. ..... Rochester
Drucker, Franklin G. ..... Bigfork
† Dube, William J. ..... Rochester
† Du Boff, Stuart M. ..... Rochester
† Dubois, David D. ..... Rochester
Dubois, Julian F. ..... Sauk Center
Duffy, John C. ..... Minneapolis
Dummer, Donald J. ..... New Brighton
Dumoneaux, Roland G. ..... Minneapolis
Duncan, Donald A. ..... Minneapolis
Duncan, James W. ..... Moorhead
† Dunham, Charles K. ..... Rochester
† Dunham, Tom R. ..... Rochester
Dunlap, David J. ..... Minneapolis
Dunlap, Earl H. ..... Minneapolis
Dunn, James P. ..... St. Paul
Dunn, Robert C. ..... St. Paul
† Dunn, Robert J. ..... Nashville, TN
Dunstan, Paul L. ..... Willmar
Dupont, Joseph A. ..... Excelsior
† Dupree, Emmett L. ..... Rochester
† Durie, Brian G. M. ..... Rochester
Durkin, John L. ..... St. Paul
Duryea, Willis M. ..... Minneapolis
Duryea, Willis M., Jr. ..... Minneapolis
Duthoy, Everette J. ..... St. Paul
Duvall, Arndt J., III ..... St. Paul
Dvorak, Benjamin A. ..... Minneapolis
Dwan, Paul F. ..... Minneapolis
† Dworsky, Samuel D. ..... Minneapolis
Dwyer, John J. ..... Duluth
Dyck, Peter J. ..... Rochester
Dyer, John Allen ..... Rochester
Dyrdal, Paul J. ..... St. Paul
Dysterheft, Adolf F. ..... Gaylord
Dzuibinski, Emil H. ..... St. Cloud

E

Earl, George A. ..... St. Paul
Earl, John R. ..... St. Paul
Earl, Stephan H. ..... Minneapolis
Eaton, David B. ..... Worthington
Eberley, Tobe S. ..... Benson
Ebert, Richard V. ..... Minneapolis
Echols, William J. ..... Selma, AL
Eckdale, John E. ..... Mankato
Eckelberg, Merlyn E. ..... APO, NY
Eckerly, Jean R. ..... Minneapolis
Eckert, Joseph F. ..... Mankato
Eckman, Matthew J. ..... Duluth
Eckman, Philip F. ..... Duluth
Eckman, Philip L. ..... Duluth
Eckman, Ralph J. ..... Duluth
† Eckstein, John D. ..... Rochester
Eder, Walter P. ..... Minneapolis
Edin, Andrew ..... Minneapolis
Edmondson, Hugh A., Jr. ..... Minneapolis
Edwards, Laura E. ..... St. Paul
Edwards, J. Willard ..... St. Paul
Edwards, Jesse E. ..... St. Paul
Edwards, Lloyd G. ..... St. Paul
† Edwards, Richard B. ..... St. Paul
Edwards, Thomas J. ..... St. Paul
† Edwards, Walter G., Jr. ..... Bethesda, MD
Edwardson, Phillip L. ..... St. Paul
Eelkema, Herman H. ..... St. Paul
Efteland, Myles E. ..... Minneapolis
† Egan, Ernest L. ..... Rochester
Egge, Sanford G. ..... Albert Lea
Eggert, Delmer C. ..... Mankato
Eginton, Charles T. ..... Fargo, ND
† Ehrenberg, Claude J. ..... Boca Raton, FL
Ehrlich, S. Paul ..... Minneapolis
Eich, Matthew A. ..... Minneapolis
Eichelberger, Dale L. ..... Willmar
Eichenlaub, John E. ..... Minneapolis
Eichhorn, Edmund P., Jr. ..... Minneapolis
Eide, O. A. ..... Hancock
† Eiden, Vera M. ..... Afton
Eilers, Vincent E. ..... St. Paul
† Eilers, William B. ..... Redwood Falls
Eisenbeis, Charles F. ..... Mankato
Eisenman, Walter ..... Hibbing
*† Eisenstadt, David H. ..... Minneapolis
Eisenstadt, William S. ..... Minneapolis
Eitel, George D. ..... Minneapolis
Eklund, Carl D. ..... Duluth
† Elkins, Earl C. ..... Rochester
† Ellerby, Richard A. ..... Rochester
Ellertson, Leonard M. ..... Albert Lea
Ellinger, Albert J. ..... Willmar
Ellingson, Richard B. ..... Minneapolis
Ellington, Anna L. ..... Minneapolis
Elliott, Harold J. ..... Hayfield
Elliott, J. W. ..... Mankato
† Elliott, Frederick W. ..... Rochester
Elliott, William G. ..... Bettendorf, IA
Ellis, Cassius M. C. ..... Minneapolis
Ellis, Earl W. ..... Elgin
Ellis, John C., Jr. ..... Minneapolis
Ellis, Ronald W. ..... St. Paul
Ellison, Evan S. ..... Minneapolis
† Ellison, Frank E. ..... Monticello
Ellwood, Paul M., Jr. ..... Minneapolis
† El Shahawy, Mahfouz A. ..... Rochester
Elumba, Teodoro V. ..... St. Paul
Emanuel, Karl W. ..... Duluth
Emerson, Edward C. ..... St. Paul
Emerson, Edwin E. ..... Osakis
Emerson, Robert K. ..... Laredo, TX
† Emmett, John L. ..... Rochester
† Emmons, Patricia R. ..... Rochester
Emmons, Robert W. ..... St. Paul
† Emmons, William F. ..... Vancouver, Canada
† Emond, Joseph S. ..... Farmington
Emond, Joseph S., Jr. ..... Farmington
Emslander, Richard F. ..... Rochester
Endress, Edward K. ..... St. Paul
† Engberg, Edward J. ..... Faribault
Engebretson, Paul ..... Alexandria
Engel Andrew G. ..... Rochester
Engel, Joseph P. ..... Minneapolis
† Engelberg, Jerry ..... Rochester
† Engels, Edward P. ..... Marshall
Engelsgjerd, Gerald L. ..... Duluth
Engelstad, Wendell P. ..... Eveleth
England, Rodney W. ..... St. Paul
Englund, Elvin F. ..... Minneapolis
† Engstrand, Oscar J. ..... Minneapolis
Engstrom, E. Duane ..... Minneapolis
Engstrom, George ..... St. Peter
Engstrom, Robert B. ..... Mankato

Engwall, Richard L. ..... Minnetonka
Enroth, Oscar E. ..... St. Paul
Erdal, Ove A. ..... Albert Lea
Erich, John B. ..... Rochester
† Erickson, Alvin O. ..... Long Prairie
Erickson, Carlton ..... Lindstrom
Erickson, Clifford O. ..... Minneapolis
Erickson, Donald J. ..... Rochester
Erickson, Donald L. ..... St. Paul
Erickson, Laurence F. ..... Minneapolis
Erickson, Myron E. ..... Minneapolis
† Erickson, Reuben F. ..... Minneapolis
Erickson, Robert L. ..... Rosemount
Erickson, Vernon D. ..... Grand Rapids
Erlanson, A. Cornell ..... St. Paul
Erling, Carl B. ..... St. Paul
† Errico, James M. ..... Rochester
† Ersek, Robert A. ..... Minneapolis
Ersfeld, Murray P. ..... St. Paul
† Erwin, Donald T. ..... Rochester
Esclius, Erik P. ..... Minneapolis
Esensten, Sidney ..... Minneapolis
Espelien, Alan D. ..... St. Cloud
Espinosa, Raul E. ..... Rochester
Estrem, Ralph L. ..... Fergus Falls
Estrem, Robert D. ..... Fergus Falls
† Ettinger, David S. ..... Rochester
Ettinger, Milton G. ..... Minneapolis
† Etzell, Paul S. ..... Rochester
Etzwiler, Donnell D. ..... Minneapolis
Eustermann, John J. ..... Mankato
† Evans, Edward T. ..... Minneapolis
Evans, Leslie M. ..... Sauk Rapids
† Evans, Titus C., Jr. ..... Rochester
Evensta, John B. ..... Grand Rapids
Everhart, Clarence E., Jr. ..... Minneapolis
Evison, Emerson O. ..... Duluth
Ewens, George B. ..... Virginia

F

Facer, George W. ..... Rochester
† Fallon, Virgil T. ..... Minneapolis
Falls, John L. ..... Red Wing
Farber, Abigail F. ..... Minneapolis
Faber, John E. ..... Rochester
Farber, Lawrence A. ..... Minneapolis
Farber, Roger E. ..... Minneapolis
* Farkas, John V. ..... St. Paul
Farley, Harrison H. ..... Minneapolis
Farr, John D. ..... St. Paul
† Farrell, Kenneth H. ..... Rochester
Farrell, T. Edwin ..... Minneapolis
Farrow, George M. ..... Rochester
Fasbender, Herman T. ..... Hastings
Faul, Bennie C. ..... Worthington
Faulconer, Albert, Jr. ..... Rochester
Faust, John H. ..... Northfield
† Fawcett, Arthur M. ..... Renville
Fawcett, Keith R. ..... Duluth
Fay, Thomas M. ..... Oakland, CA
Fedders, Skaidrite ..... Willmar
Fedor, Robert ..... Willmar
Fee, John G. ..... St. Paul
*† Feeney, John M. ..... Excelsior
† Fehrenbaker, Lawrence G. ..... Rochester
Feigal, David W. ..... Wayzata
Feigal, Gary R. ..... Lake City
Feigal, William M. ..... Fairmont
† Feinberg, Jack H. ..... Rochester
Feinberg, Philip ..... Minneapolis
Feinberg, Samuel B. ..... Minneapolis
† Feintuch, Theodore A. ..... Rochester
Felder, Davitt A. ..... St. Paul
Feldmann, Floyd M. ..... Pompano Beach, FL
Felion, Arthur J. ..... St. Paul
Fellows, Manley F. ..... Duluth
Fenske, Arnold W. ..... Winona
Ferguson, John N. ..... St. Paul
Ferguson, Richard H. ..... Rochester
Fernandez, Rafael F., Jr. ..... Minneapolis
Ferris, Deward O. ..... Rochester
Fesenmaier, Otto B. ..... Los Angeles, CA
† Fesler, Harold H. ..... W. St. Paul
Fetzek, Albert D. ..... Minneapolis
Feuling, John C. ..... Sun City, AZ
Field, Charles W. ..... Hopkins
Fifer, Ellen Z. ..... St. Paul
Fifer, William R. ..... Minneapolis
Fifield, Malcolm M. ..... Duluth
Filiatrault, L. J. ..... Coon Rapids
Filipovich, Orest N. ..... Minneapolis
Fingerman, David L. ..... Minneapolis
Fink, Daniel L. ..... St. Paul
† Fink, Lawrence H. ..... Silver Spring, MD
† Fink, Leo W. ..... Minneapolis
† Fink, Richard A. ..... Rochester
Fink, Robert J. ..... Minneapolis
Finkelnburg, William O. ..... Winona
Finkelstein, Joel ..... Rochester
Finkelstein, Sidney ..... Minneapolis
Finlayson, Richard E. ..... Minneapolis
† Fischer, Albert P. ..... Wayzata
Fischer, Robert F. ..... St. Paul
Fish, Charles R. ..... Rochester
Fisher, Don H. ..... Minneapolis
Fisher, Isadore I. ..... Minneapolis
Fisketti, Henry ..... Duluth
Fitch, Charles G. ..... Worthington
† Fitz, Frederick W. ..... Rochester
Fitzsimons, William E. ..... Brainerd
† Fitzpatrick, Patrick J. ..... Rochester
† Fitzgerald, Robert H., Jr. ..... Rochester
† Flancher, Leon H. ..... Detroit Lakes
Flanagan, Kathleen R. ..... St. Paul
Flanigan, Donald J. ..... Pensacola, FL
Flannery, Hubert F. ..... St. Paul
Fleming, Dean S. ..... Minneapolis
† Fleming, Martin P. ..... Rochester
Flick, William F. ..... Rochester
Fliehr, Richard R. ..... Minneapolis
Flinn, James B. ..... Redwood Falls
Floersch, Adrian J. ..... Owatonna
Flom, Reynold P. ..... St. Paul
Flom, Robert S. ..... St. Paul
Flora, George C. ..... Minneapolis
† Florence, David W. ..... Minneapolis
Florine, Martin C. ..... Madison Lake
Flory, William D. ..... Minneapolis
Fluegel, John O. ..... Minneapolis
Flynn, Bernard F. ..... Hibbing
Flynn, Louis L., Jr. ..... St. Paul
Flynn, Robert A. ..... St. Paul
Foderick, John W. ..... Hastings
Foderick, Peter P. ..... Ada
Fogelberg, Emil J. ..... St. Paul
Foker, Leslie W. ..... Minneapolis

Foley, Robert R. ....Minneapolis
† Foley, Thomas F. ....Rochester
Foley, William A. ....Minneapolis
Folsom, Louis B. ....Minneapolis
Fontana, Robert S. ....Rochester
Forbes, Edward F. ....Minneapolis
† Ford, Burton C. ....Marshall
Ford, W. Harold ....Hopkins
Foreman, Richard T. ....St. Paul
Forker, Alan D. ....Coronado, CA
Forsythe, James R. ....St. Paul
Fortier, George M. A. ....Little Falls
Fortier, George M. A., Jr. ....Little Falls
Fortier, Rene G. ....Mankato
Fortuny, Ignacio E. ....Minneapolis
† Foss, Edward L. ....Condon, MT
Foster, Orley W. ....Minneapolis
† Foster, Thomas N., III ....Rochester
Foulk, William T., Jr. ....Rochester
Fowler, Franklin, Jr. ....APO San Francisco, CA
Fox, James Rogers ....Minneapolis
Fox, John A. ....Ft. Dix, NJ
Fox, LeRoy J. ....St. Paul
Fraley, Elwin E. ....Minneapolis
† Franchere, Frederick W. ....Lake Crystal
Francis, David W. ....Morristown
Frane, Donald B. ....Minneapolis
Frane, Gerald T. ....Minneapolis
Franklin, Gordon W. ....Northome
† Frederickson, Alice C. ....Willmar
Fredlund, Jon S. ....Anoka
† Freedman, Harvey M. ....Rochester
Freel, Robert J. ....Lackland AFB, TX
Freeman, Charles D., Jr. ....St. Paul
Freeman, Craig W. ....Minneapolis
Freeman, Donald W. ....St. Louis Park
† Freeman, Richard E. ....Rochester
French, Bayard T. ....Hibbing
French, Lyle A. ....Minneapolis
Frethem, Allen A. ....Rochester
Frey, Richard J. ....Minneapolis
Friberg, Joseph B. ....Minneapolis
† Fricke, Robert E. ....Rochester
Fried, Louis A. ....Minneapolis
† Friedell, Aaron ....Minneapolis
Friedell, George ....Minneapolis
Friedlieb, Oskar P. ....Virginia
Friedman, Harry S. ....Minneapolis
Friedrich, Bradford E. ....Red Wing
Friend, Charles A. ....Minneapolis
† Fritsche, Albert ....New Ulm
Fritsche, Carl J. ....New Ulm
Fritsche, Theodore R. ....New Ulm
Fritz, Wallace L. ....St. Paul
† Froats, Charles W. ....St. Paul
Frost, John B. ....Minneapolis
Frost, John W. ....St. Paul
Fruchtman, Stanley A. ....Minneapolis
Frye, Charles W. ....St. Paul
Frys, Russell N. ....Minneapolis
† Frytak, Stephen ....Rochester
Fuglestad, Edson V. ....Minneapolis
Fuglestad, J. Roald ....Minneapolis
† Fuller, Alice H. ....Minneapolis
Fuller, Benjamin F. ....White Bear Lake
† Fuller, Edwin B. ....Rochester
Fuller, Josiah ....Duluth
† Funk, Victor K. ....Hopkins
Funke, Joyce L. ....St. Paul
Furlow, William L. ....Rochester
Furman, L. Christine ....Minneapolis
Furr, Leo ....Bird Island
† Furszyfer, Jacob ....Rochester

G

Gaard, Richard C. ....Robbinsdale
Gaebe, Milton B. ....Clara City
Gaertner, Frank M. J., Jr. ....St. Paul
Gaertner, John R. ....St. Paul
Gaida, Joseph B. ....St. Cloud
Gailitis, Veronika M. ....St. Paul
Galbraith, Richard F. ....Minneapolis
Galejs, Aina ....St. Paul
Gallagher, Larry J. ....Mound
Gallett, Lester E. ....Minneapolis
Galligan, John J. ....St. Paul
† Galligan, Margaret Mary D. ....Minneapolis
Galloway, Jackson R. ....Alexandria, LA
Galway, Charles F. ....St. Paul
† Gambill, Carl M. ....Rochester
Gambill, Earl E. ....Rochester
Gamble, Elbert J. ....Roseville
Gamble, William G. ....Minneapolis
Gamm, Edgar R. ....Park Rapids
Gannon, Paul G. ....Minneapolis
Garamella, Joseph J. ....Minneapolis
Garber, George L. ....Winona
Garber, James J. ....Rochester
Gardner, Jack K. ....Fairmont
† Gardner, Victor H. ....Fairmont
Gardner, Walter P. ....St. Paul
Garetz, Floyd K. ....Minneapolis
Garrick, James G. ....Bethesda, MD
Garrow, Douglas M. ....St. Paul
Garske, George L. ....Minneapolis
Garten, Joseph L. ....Minneapolis
Garvey, James T. ....Minneapolis
Gasik, Joseph M. ....Minneapolis
Gastineau, Clifford F. ....Rochester
Gaute, Svend T. ....St. Paul
Gaviser, David ....Minneapolis
Gedgaudas, Eugene ....Minneapolis
† Gehlen, Joseph N. ....St. Paul
Geib, Marvin J. ....Fargo, ND
Geis, LeRoy F. ....Fargo, ND
Geiser, Peter M. ....Alexandria
Geist, Robert W. ....St. Paul
Geller, Joseph ....Minneapolis
Gendron, Joseph L. ....St. Paul
Gentling, Peter A. ....San Diego, CA
George, Vane P., Jr. ....LeSueur
Geraci, Joseph E. ....Rochester
Gerend, Thomas J. ....Virginia
Gerstenkorn, George B. ....Milaca
Gerster, Paul W. ....Anoka
Gesundheit, Sim ....Minneapolis
Geurs, Benjamin R. ....Mankato
† Ghostley, Mary C. ....Bemidji
Gibbs, Edward C. ....St. Paul
Gibbs, Robert W. ....Minneapolis
Giebenhain, John N. ....Minneapolis
† Giere, Joseph C. ....Minneapolis
† Giere, Richard W. ....Minneapolis

† Giere, Silas W. ..... Benson
† Gifford, William A. ..... Rochester
Gilbert, Maurice G. ..... Minneapolis
Gilbertsen, A. Sigrid ..... Minneapolis
Gilbertsen, Victor A. ..... Minneapolis
Gilchrist, Milton R. ..... St. Paul
Gildersleeve, John W. ..... Ft. Sam Houston, TX
Gildersleeve, Robert G. ..... Watertown
Gill, Theodore M. ..... Albert Lea
Gilles, Paul J. ..... Minneapolis
Gilles, Thomas F. ..... Fairfax
Gillespie, Delmar R. ..... St. Paul
† Gillespie, Malcolm G. ..... Duluth
Gilman, Lloyd C. ..... Willmar
Gilsdorf, Donald A. ..... St. Paul
† Gingold, Benjamin A. ..... Minneapolis
Gislason, Paul H. ..... Mankato
Gisvold, John J. ..... Rochester
Gjerde, William P. ..... Lake City
Glaeser, John H. ..... Minneapolis
Glenny, William R. ..... St. Paul
Glick, Dallas D. ..... Mountain Lake
Glomstad, Gary B. ..... Grand Rapids
† Goblirsch, Andrew P. ..... Sleepy Eye
Godfrey, H. Wilson ..... Minneapolis
Goehl, Reinhold O. ..... Minneapolis
Goehrs, Gilman H. ..... St. Cloud
† Goellner, John R. ..... Rochester
Goetz, Frederick C. ..... Minneapolis
Gokcen, Barbara W. ..... Minneapolis
Gokcen, Muharrem ..... Minneapolis
Gold, Ernest M. ..... St. Paul
† Goldberg, Isadore M. ..... Minneapolis
Goldberg, Marvin E. ..... Minneapolis
Goldberg, Robert J. ..... St. Paul
Goldberg, Stanley M. ..... Minneapolis
Goldfarb, Benjie L. ..... Minneapolis
Goldfarb, Mace G. ..... Minneapolis
Goldish, Daniel R. ..... Duluth
Goldish, Robert J. ..... Duluth
† Goldman, Theodore I. ..... Minneapolis
Goldner, Meyer Z. ..... Minneapolis
Goldschmidt, Volker ..... Duluth
Goldsmith, Joseph W. ..... St. Paul
Goldstein, Alan L. ..... Hopkins
Goldstein, Norman P. ..... Rochester
Goldston, Edgar C. ..... Rochester
Good, C. Allen, Jr. ..... Rochester
Good, Gary ..... Minneapolis
Good, Roy H. ..... Northfield
Goodchild, William R. ..... Minneapolis
Goodale, Robert L., Jr. ..... Minneapolis
Goodall, David C. ..... Deer River
Goodman, Ernest ..... St. Paul
Goodnow, William H. ..... Duluth
† Goodwin, Henry N. ..... Rochester
Goott, Bernard ..... St. Paul
Gordon, John R. ..... Minneapolis
Gordon, Sewell S. ..... Minneapolis
Gorman, Columba A. ..... Rochester
Gould, Allan B., Jr. ..... Rochester
† Gould, Barry K. ..... Rochester
† Gould, Ronauld J. ..... Rochester
Govrik, Kalman ..... St. Paul
Gowan, Lawrence R. ..... Duluth
Gowan, Lawrence R., Jr. ..... Duluth
Gozum, Ekrem ..... Minneapolis
Grabow, Jack D. ..... Rochester
Grados, Carlos ..... Coon Rapids
Graf, John A. ..... Rochester
Grage, Theodor B. ..... Minneapolis
Graham, Asa B. ..... Faribault
Graham, John J. ..... Minneapolis
Grahek, Jack P. ..... Ely
† Gran, Gary E. ..... Rochester
Grande, David W. ..... Mankato
Granquist, Richard D. ..... Minneapolis
Grant, James B. ..... Minneapolis
Grant, John C. ..... Sauk Centre
Grant, Suzanne ..... Minneapolis
† Gratzek, Frank R. ..... Anoka
Gravett, Desmond C. ..... Rochester
† Gray, Royal C. ..... Minneapolis
Gredcn, John F. ..... Silver Springs, VA
Green, Clayton R. ..... Excelsior
Green, John F. ..... Alexander
Green, Paul A. ..... Rochester
Green, Robert A. ..... Minneapolis
Greenberg, Albert J. ..... Minneapolis
Greene, Gordon ..... Hibbing
Greene, Jerry G. ..... St. Paul
Greene, Laurence F. ..... Rochester
Greene, Leonard H. ..... Minneapolis
Greenfield, Irving ..... Minneapolis
Greenwald, Stephen M. ..... Minneapolis
Gregoire, Earl ..... Bemidji
¶ Greisheimer, Esther M. ..... Philadelphia, PA
Gretsch, Gerald A. ..... St. Paul
Gridley, John W. ..... St. Paul
Griebie, Grant L. ..... Hutchinson
Griffin, John W. ..... Bemidji
Griffin, Patrick J. ..... St. Paul
Griffin, Richard P. ..... Benson
Griffin, Thomas M. ..... St. Paul
Griffiths, Robert W. ..... El Paso, TX
Grimes, Burton P. ..... St. Peter
Grimes, Marian ..... Minneapolis
Grimes, Paul T. ..... Park Rapids
Grimmell, Francis J. ..... Minneapolis
Grinley, Andrew V. ..... Grand Rapids
Grinvalds, Anna O. ..... Cambridge
† Grismer, Jerome T. ..... Wauwatosa, WI
Grohs, William H. ..... Duluth
Gronquist, Y. K. J. ..... Cloquet
Groover, Robert Vann ..... Rochester
*† Groschupf, Theophilus P. ..... Bemidji
Grose, Frederick N. ..... Clarissa
Gross, John B. ..... Rochester
Grossling-Freudenburg, Sergio ..... Rochester
Grubbs, Larry T. ..... Rochester
Grube, David W. ..... Minneapolis
Gruys, Robert I. ..... Minneapolis
Gudio, Felix A., Jr. ..... St. Paul
Guerrero, Rafael A. ..... Minneapolis
Guilfoile, Pierre J. ..... Delano
Guiser, Lynn G. ..... White Earth
Gullickson, Glenn, Jr. ..... Minneapolis
Gumnit, Robert J. ..... St. Paul
† Gunderson, David H. ..... Rochester
Gunlaugson, Frederick G. ..... Minneapolis
Gustafson, Paul O. ..... Minneapolis
Gustafson, Robert W. ..... Granite Falls
Gustason, Harold T. ..... Minneapolis
Gustilo, Ramon B. ..... Minneapolis
Guthrie, J. Cameron ..... St. Paul
Gutzmann, Bruce W. ..... Faribault
Guy, Jack A. ..... New London

H

Haas, Jack F. ..... Northfield
Haas, John W. ..... Minneapolis
† Haakenson, Robert C. ..... Rochester
Haase, Donald D. ..... Silver Bay
Haavik, John E. ..... Duluth
† Habein, Harold C. ..... Palo Alto, CA
Haberer, Helen R. ..... Stacy
Haberle, Charles A. ..... Minneapolis
† Hable, Kathleen A. ..... Rochester
† Haddad, Nickie J. ..... Rochester
† Haddad, Paul G. ..... Rochester
† Haes, Julius E. ..... St. Peter
Haesly, Warren W. ..... Winona
Hagberg, Norman L. ..... Montevideo
Hagedorn, Albert B. ..... Rochester
Hagen, John D. ..... Austin
Hagen, Kristofer ..... Minneapolis
Hagen, Wayne S. ..... Minneapolis
Haglin, John J. ..... Minneapolis
Hahn, Richard G. ..... Rochester
† Haines, Samuel F. ..... Rochester
Hakanson, Erick Y. ..... St. Paul
Hakim, Ali A. ..... Minneapolis
Halbert, John J. ..... Duluth
† Halenbeck, Philip L. ..... St. Cloud
Hall, Arthur M. ..... Minneapolis
Hall, Barnard ..... St. Paul
Hall, Harry B. ..... Minneapolis
Hall, Loren J. ..... Minneapolis
Hall, Wendell H. ..... Minneapolis
† Hallberg, Olav Erik ..... Rochester
Hallgren, Roger B. ..... Belle Plaine
Halliday, Phillip V. ..... Duluth
Hallin, Roger P. ..... Worthington
† Halloran, Walter H. ..... Jackson
Halme, William B. ..... Wadena
Halper, Bernard ..... Hibbing
Halpern, David J. ..... Brewster
Halverson, Kermit J. ..... Parkville
Halverson, William G. ..... Madelia
Halvorsen, Daniel K. ..... Owatonna
Halvorson, David C. ..... Northfield
Halvorson, Harold C. ..... Albert Lea
Halvorson, James W. ..... Zumbrota
Ham, O. Emerson, Jr. ..... San Antonio, TX
Hambidge, Gove, Jr. ..... Minneapolis
Hamel, Arnold L. ..... Minneapolis
Hamel, Joseph I. ..... Minneapolis
Hammar, Lawrence M. ..... Mankato
† Hammargren, Lonnie L. ..... Rochester
Hammerstrom, Robert N. ..... Minneapolis
Hammes, Ernest M., Jr. ..... St. Paul
† Hancock, William E. ..... Rochester
Handler, Seymour ..... Minneapolis
Hanisch, Edward C., Jr. ..... Minneapolis
Hankerson, Robert G. ..... Mankato
Hanlon, David G. ..... Rochester
Hannon, Donald W. ..... St. Paul
Hanover, Ralph D. ..... International Falls
Hansen, Cyrus O. ..... Minneapolis
† Hansen, Erling W. ..... Minnetonka
Hansen, Milo L. ..... Little Falls
† Hansen, Olga S. ..... Minneapolis
Hansen, Robert E. ..... Hibbing
Hansen, Rollin M. ..... Minneapolis
Hansen, Theodore M. ..... Albert Lea
Hanske, Edward A. ..... Minneapolis
Hanson, Ernest O. ..... Cloquet
Hanson, Everett C. ..... New York Mills
† Hanson, Harlow J. ..... Minneapolis
Hanson, Harold B. ..... Burnsville
Hanson, Harold W. ..... Minneapolis
† Hanson, Henry V. ..... Green River, AZ
Hanson, Lewis ..... Frost
† Hanson, Malcolm B. ..... Osseo
Hanson, Mark C. L. ..... Minneapolis
Hanson, Mildred S. ..... Minneapolis
Hanson, Norbert O. ..... Rochester
Hanson, Stephen L. ..... Minneapolis
† Hanson, William A. H. ..... Minnetonka
Hanson, William B. ..... Minneapolis
Hanton, Edward M. ..... St. Paul
Harbaugh, John T. ..... St. Cloud
† Harbold, Norris B., Jr. ..... Rochester
† Harder, Edward J. ..... Rochester
† Hargraves, Malcolm M. ..... Rochester
Harmon, Gaius E. ..... St. Paul
Harper, David G. ..... Duluth
† Harrington, Donald P. ..... Minneapolis
† Harrington, Stuart W. ..... Rochester
Harrington, Vernon A. ..... Duluth
Harris, John E. ..... Minneapolis
Harris, Leon D. ..... Minneapolis
Harris, Max E. ..... St. Paul
Harrison, Percy W. ..... Worthington
Harrison, William C. ..... Minneapolis
† Hart, William E. ..... Monticello
Hartfiel, William F. ..... St. Paul
Hartfield, James E., Jr. ..... Rochester
Hartig, Marjorie ..... St. Paul
Hartig, Paul R. ..... Minneapolis
Hartman, Evelyn E. ..... Minneapolis
Hartnagel, Grant F. ..... Red Wing
Hartung, Elmer H. ..... Claremont
Hartwich, Roger F. ..... Winona
Hartwig, John A. ..... Minneapolis
Harty, Jerome L. ..... Minneapolis
Hartzell, Allan J. ..... Duluth
Hartzler, Paul L. ..... Cambridge
Harvey, Clyde B. ..... Minneapolis
Hass, Frederick M. ..... Minneapolis
Hastings, Donald W. ..... Minneapolis
Hastings, John D. ..... Denver, CO
Hauge, Erling T. ..... Minneapolis
† Hauge, Malvin I. ..... Marcell
Haugen, George W. ..... Minneapolis
Haugen, John A. ..... Minneapolis
Haus, Erhard ..... St. Paul
Hauser, Charles W. ..... St. Paul
Hauser, Donald C. ..... Minneapolis
† Hauser, Victor P. ..... St. Paul
Havel, Robert J. ..... Minneapolis
Haven, Walter K. ..... Minneapolis
Havig, Terrance A. ..... Lubbock, TX
Hawk, Dale J. ..... St. Charles
Hawkinson, Harlan W. ..... St. Paul
† Hawkinson, Raymond P. ..... Minneapolis
Hawley, George M. B., II ..... Red Wing
Hay, Lyle J. ..... Minneapolis
† Hayashi, Melvin M. K. W. ..... Rochester
Hayes, Albert F. ..... St. Paul
Hayles, Alvin B. ..... Rochester
Hays, Albert T. ..... Minneapolis

Hays, James C. ..... Jackson, MI
Haywa, E. William ..... Minneapolis
Hazen, Richard W. ..... Willmar
† Head, Douglas P. ..... Minneapolis
Heagle, C. Russell ..... Waconia
Hebbel, Robert ..... Minneapolis
† Hebeisen, Milton B. ..... Chaska
† Heck, Frank J. ..... Rochester
† Heck, William W. ..... St. Paul
Hedemark, Homer H. ..... Ortonville
† Hedemark, Truman A. ..... Ortonville
Hedenstrom, Charles W. ..... St. Paul
† Hedenstrom, Frank G. ..... St. Paul
Hedenstrom, Philip C. ..... Marshall
Hedenstrom, Richard H. ..... St. Paul
† Hedlund, Charles J. ..... St. Paul
Hedrick, William L. ..... Minneapolis
Heegaard, William G. ..... Alexandria
Hegrenes, Robert L. ..... Hutchinson
Hegstad, Thomas C. ..... Windom
† Heiam, William C. ..... Cook
Heiberg, Olaf M. ..... Worthington
Heid, James K. ..... Little Falls
† Heidel, Werner ..... Cresskill, NJ
Heimark, John J. ..... Mankato
† Heinberg, Charles E. ..... Rochester
Heinz, Ivy B. ..... Shakopee
Heinz, John N. ..... Minneapolis
† Heinzer, Francois C. ..... Rochester
Heinzerling, Carl R. ..... Chaska
Heise, Carl vR ..... Winona
Heise, Herbert vR ..... Winona
Heise, Paul vR ..... Winona
Heise, William vR ..... Winona
Heisel, John G. ..... Duluth
Held, William J. ..... St. Cloud
† Helgason, Pall B. ..... Rochester
Heller, Edgar E. ..... Mankato
Helmholz, Henry F., Jr. ..... Rochester
† Helseth, Hovald K. ..... Fergus Falls
Helwig, Karl L. ..... Virginia
Hempel, Dean J. ..... Minneapolis
Henderson, Edward D. ..... Rochester
Henderson, John W. ..... Rochester
Henderson, Lowell L. ..... Rochester
Henderson, Terrance P. ..... White Bear Lake
† Hendricks, John L. ..... Rochester
† Hengstler, William H. ..... St. Paul
Henke, Clarence Earl ..... Rochester
Henke, Wilbert J. ..... St. Paul
Henrikson, Earl C. ..... Minneapolis
† Henry, Clarence J. ..... Onamia
Henry, Harold W. ..... Moose Lake
Henry, James S. ..... St. Paul
Henry, John C. ..... Owatonna
Henry, Joseph E. ..... Milaca
Henry, Kenneth G. ..... Owatonna
Hepper, Norman G. ..... Rochester
Herber, Leo ..... Thief River Falls
† Herbert, Willis L. ..... Minneapolis
Hergott, Patrick F. ..... Waseca
Herland, Alexander L. ..... Winona
† Herman, Peter S. ..... Rochester
Herman, Samuel M. ..... St. Paul
Hermans, Paul E. ..... Rochester
Herrick, Donald W. ..... St. Paul
† Hertel, Garfield E. ..... McAllen, TX
Hesla, Inman A. ..... Austin
Hess, Carroll N. ..... Minneapolis
† Hetzler, John A. ..... White Bear Lake
Heupel, Hermann W. ..... Minneapolis
† Hewitt, Edith S. ..... Rochester
Hewitt, Marshall I. ..... Minneapolis
*† Hewitt, Richard M. ..... Rochester
Hiatt, John A. ..... Minneapolis
Hickok, David F. ..... Minneapolis
Hick, John F. ..... Winona
Hildebrand, John E. ..... Bemidji
Hildebrandt, Walter C. ..... Minneapolis
Hilding, Anderson C. ..... Duluth
Hildreth, Thomas A. ..... San Francisco, CA
Hilgedick, William R. ..... Minneapolis
Hilger, Jerome A. ..... St. Paul
Hilger, Laurence D. ..... St. Paul
Hilgers, Robert D. ..... St. Paul
Hilgermann, George O. ..... Minneapolis
Hilker, Marcus D. ..... St. Paul
Hilker, Robert T. ..... Owatonna
Hill, Charlotte W. ..... St. Paul
Hill, Earl ..... Minneapolis
Hill, Elmer M. ..... Minneapolis
Hill, John R. ..... Rochester
† Hill, Richard W. ..... Rochester
† Hill, Wayne A. ..... Rochester
Hiller, Bruce H. ..... Minneapolis
† Hiller, Erhard ..... Rochester
Hinckley, Robert G. ..... White Bear Lake
Hinderaker, Harris P. ..... Willmar
Hines, Edgar A., Jr. ..... Brevard, NC
† Hiniker, Louis P. ..... St. Paul
† Hiniker, Peter J. ..... St. Peter
Hinz, Walter E. ..... Willmar
Hippchen, Ray C. ..... St. Paul
Hirsh, Stanton A. ..... Crookston
Hitchcock, Claude R. ..... Minneapolis
Ho, Shu Kang ..... St. Paul
Hoagland, H. Clark ..... Rochester
Hodapp, Robert V. ..... Willmar
Hodges, Kenneth V. ..... Minneapolis
Hodgson, Corrin H. ..... St. Paul
Hodgson, Jane E. ..... St. Paul
Hodgson, John R. ..... Rochester
† Hodgson, Stephen F. ..... Rochester
Hoeg, Dwight C. ..... Duluth
† Hoehn, James G. ..... Rochester
† Hoeper, Philip G. ..... Chestnut Hill, MA
Hoff, Herbert O. ..... Duluth
Hoffert, Henry E. ..... Minneapolis
† Hoffman, Roy A. ..... Minneapolis
Hoffman, Walter Lees ..... Minneapolis
Hofmann, Gerald N. ..... Minneapolis
Hoganson, Donald E. ..... Bemidji
Hohmann, Albert ..... St. Paul
Holbrook, Margaret A. ..... Rochester
† Holcomb, Joel T. ..... Marine-on-the-St. Croix
*† Holcomb, O. William ..... St. Paul
Holland, C. R. ..... Rochester
Hollenhorst, Robert W. ..... Rochester
Hollinshead, W. H. ..... St. Paul
† Holm, Jan ..... Rochester
Holm, Donald F. ..... Minneapolis
Holm, Owen W. ..... Hibbing
Holman, Colin B. ..... Rochester
Holmberg, Conrad J. ..... Minneapolis
Holmstrom, Carle H. ..... Warren
Holt, Glen E. ..... Duluth
† Holt, John E. ..... St. Paul

Holten, David R. ..... Minneapolis
Holten, John ..... Moorhead
Holzapfel, Fred C. ..... Minneapolis
Hom, Leong Y. W. ..... Fergus Falls
Honath, Donald H. ..... Owatonna
Hood, Roderick P. ..... Duluth
Hoover, Norman W. ..... Chicago, IL
Hopkins, G. Wendell ..... Minneapolis
Hopperstad, J. Jerome ..... Minneapolis
Hoppes, Emerson E. ..... Minneapolis
Horecki, Henry ..... Minneapolis
Horns, Howard L. ..... Minneapolis
Horns, Norman ..... Minneapolis
Horns, Richard C. ..... Minneapolis
Horowitz, Arthur J. ..... Minneapolis
† Horton, Bayard T. ..... Rochester
Hoseth, Wayne L. ..... Minneapolis
Hottinger, George C. ..... St. Paul
Hottinger, Raymond C. ..... Janesville
Houglum, Arvid J. ..... Duluth
† Houkom, Bjarne ..... Fergus Falls
Houkom, S. Sverre ..... Duluth
Houle, Rollin J. ..... New Brighton
Houlton, William H. ..... St. Paul
House, James H. ..... Minneapolis
Houser, Otis ..... Rochester
Houts, Joseph C. ..... Dassel
Hovde, Gordon W. ..... Lindstrom
Hovland, Melvin L. ..... Minneapolis
Hovland, Richard D. ..... Minneapolis
Howard, Frank M., Jr. ..... Rochester
† Howard, John D. ..... Rochester
† Howard, Richard J. ..... Edina
Howard, Solomon E. ..... Minneapolis
Howe, Newell W. ..... West St. Paul
Howell, Carter W. ..... Minneapolis
Howell, John L. ..... Minneapolis
Howell, Llewelyn P. ..... Rochester
Hoyt, C. Sherman ..... Minneapolis
Hruza, William J. ..... Sioux Falls, SD
† Hu, Chung-Hong ..... Rochester
Huber, Robert W. ..... St. Croix Falls, WI
Hubin, Edwin G. ..... Sandstone
† Hudson, Albert W. ..... Rochester
Huebert, Dan W. ..... Hutchinson
*† Huenekens, Edgar J. ..... Minneapolis
† Huerta, Enrique ..... Rochester
Huff, John S. ..... Minneapolis
Huffington, Herb L. ..... Waterville
† Huffington, Herbert L. ..... Brownsville, TX
Hughes, Bernard J. ..... St. Cloud
Hughes, Sidney O. ..... Winona
Hulteng, Donald B. ..... Minneapolis
Hunder, Gene G. ..... Rochester
Hunt, Arthur B. ..... Carmel, CA
Hunt, James C. ..... Rochester
† Hunt, Vincent R. ..... Minneapolis
Hunter, Murray H. ..... Farmington
Hunter, Samuel W. ..... St. Paul
Hurr, Maland C. ..... Minneapolis
Hurwitz, Milton M. ..... St. Paul
Huseby, Thomas L. ..... St. Paul
Husebye, Kjeld O. ..... St. Paul
Hustad, Edward G. ..... Minneapolis
† Hutchinson, Henry ..... Brainerd
† Hutchinson, James C., Jr. ..... Rochester
Hymes, Alan C. ..... Minneapolis
† Hymes, Charles ..... Minneapolis
† Hynes, Kieran M. ..... Rochester
† Hyslop, Thomas ..... Rochester

I

Ibrahim, George W. ..... Virginia
Ide, Arthur W., Jr. ..... Minneapolis
Idstrom, Linneus G. ..... Minneapolis
Indeck, Walter ..... Minneapolis
Ingalls, Edgar G. ..... Minneapolis
† Ireland, Damian C. R. ..... Rochester
† Ireland, Gerald W. ..... St. Paul
Isaacson, Ronald ..... Mathers AFB, CA
Isele, Reginald H. ..... Austin
Iverslie, Philip C. ..... Minneapolis
Iverson, Eleanor B. ..... Minneapolis
Iverson, Paul C. ..... Grand Rapids
Iverson, Rolf M. ..... Minneapolis
Ivins, John C. ..... Rochester

J

Jackish, George E. ..... Red Wing
Jacklin, Alexander J. ..... Duluth
Jackman, Raymond J. ..... Rochester
† Jackson, Charles B. ..... Rochester
Jackson, J. Albert ..... Minneapolis
Jackson, Richard L. ..... Minneapolis
Jackson, William C. ..... St. Paul
Jacobs, Douglas L. ..... Willmar
† Jacobson, Clarence ..... Chisholm
Jacobson, Clifford W. ..... Breckenridge
Jacobson, Dennis ..... Onamia
Jacobson, Ferdinand C. ..... Duluth
Jacobson, Leslie W. ..... Minneapolis
Jacobson, Loren J. ..... Minneapolis
Jacobson, Wyman E. ..... Minneapolis
Jacott, William E. ..... Duluth
Jaeger, Dwight E. ..... St. Cloud
Jaffe, Manuel O. ..... Minneapolis
James, Ellery M. ..... St. Paul
James, John W. ..... St. Paul
Janda, George W., Jr. ..... Minneapolis
Janda, Wayne E. ..... Austin, TX
† Jander, Hartwig P. ..... Rochester
Janecek, James, Jr. ..... St. Paul
Janecky, Allen G. ..... Baudette
Janes, Joseph M. ..... Rochester
Janssen, Martin E. ..... St. Paul
Jarvis, Charles W. ..... St. Paul
Jastram, Rupert M. ..... St. Paul
Jay, Alan R. ..... Temple, TX
Jefferies, William L. ..... Minneapolis
Jensen, Alvin M. ..... Brownton

† Jensen, James W. ..... Rochester
Jensen, John ..... Crookston
Jensen, Nathan K. ..... Minneapolis
Jensen, Paul A. ..... Minneapolis
Jensen, Reynold A. ..... Minneapolis
*† Jensen, Thorvold J. ..... Duluth
Jenson, James E. ..... Stillwater
Jepson, William W. ..... Minneapolis
Jerome, Bourne ..... Minneapolis
Jerome, Elizabeth B. K. ..... Minneapolis
Jeronimus, Henry J. ..... Duluth
Jessico, Charles M. ..... Duluth
Jeub, Robert P. ..... Minneapolis
† Jilek, Dennis D. ..... Rochester
Jinkins, Roger E. ..... Excelsior
John, Byron L. ..... St. Cloud
Johnson, Alan R. ..... Windom
Johnson, Aldridge F. ..... St. Paul
Johnson, Angelo G. ..... Minneapolis
Johnson, Arthur B. ..... Minneapolis
Johnson, Bradley D. ..... Minneapolis
Johnson, Calvin J. ..... Grand Rapids
Johnson, Carl Edwin ..... St. Paul
Johnson, Carl Eric ..... Rochester
Johnson, Carolyn A. ..... St. Paul
Johnson, C. Percy ..... Tyler
† Johnson, Charles L. ..... Rochester
Johnson, Curtis A. ..... Princeton
Johnson, Curtis M. ..... Winona
Johnson, Daniel A. ..... Litchfield
Johnson, Daniel T. ..... St. Paul
Johnson, David R. ..... Minneapolis
Johnson, Donald A. ..... Minneapolis
Johnson, Douglas L. ..... Brainerd
Johnson, Edward A. ..... Minneapolis
† Johnson, Einer W. ..... Bemidji
Johnson, Einer W., Jr. ..... Rochester
Johnson, Frank E. ..... Minneapolis
Johnson, Franklin L. ..... Duluth
† Johnson, Gerhard J. ..... Rochester
Johnson, Gordon E. ..... Minneapolis
Johnson, Harry A., Jr. ..... Minneapolis
Johnson, Herbert W. ..... St. Paul
† Johnson, James A. ..... Minneapolis
Johnson, John W. ..... Minneapolis
Johnson, Karl E. ..... Duluth
† Johnson, Kenneth A. ..... Rochester
Johnson, Lyle O. ..... St. Paul
Johnson, Marvin W. ..... Dassel
Johnson, Norman P. ..... Minneapolis
Johnson, Norman Paul ..... St. Paul
Johnson, Norton T. ..... Minneapolis
Johnson, O. Guy ..... St. Paul
† Johnson, Olga H. ..... Detroit Lakes
Johnson, Paul E. ..... Wayzata
Johnson, Ralph B. ..... Lanesboro
Johnson, Reinald G. ..... Minneapolis
*† Johnson, Reuben A. ..... Minneapolis
Johnson, Rex R. ..... New Ulm
Johnson, Richard J. ..... St. Paul
Johnson, Richard S. ..... Minneapolis
Johnson, Richard V. ..... Minneapolis
Johnson, Robert E. ..... Minneapolis
Johnson, Robert H. ..... St. Paul
Johnson, Roger L. ..... St. Paul
Johnson, Theodore L. ..... Duluth
Johnson, Thomas E. ..... St. Paul
Johnson, Thomas F. ..... Orlando, FL
Johnson, Thomas H., Jr. ..... Minneapolis
Johnson, Vilhelm M. ..... Dawson
† Johnson, Warren L. Jr. ..... Rochester
Johnson, William E. ..... St. Cloud
Johnson, William J. ..... Rochester
Johnson, Youbert T. ..... Minneapolis
Johnsrud, Luverne W. ..... Hibbing
Johnston, Bemis H. ..... Eatontown, NJ
Johnston, Donald K. ..... Minneapolis
Johnston, H. Wayne ..... Virginia
Johnston, Leonard F. ..... Winona
Jones, Allen M. ..... San Angelo, TX
Jones, David G. ..... Minneapolis
† Jones, H. Royden, Jr. ..... Rochester
† Jones, Herbert W., Jr. ..... Minneapolis
† Jones, Orville H. ..... Mankato
Jones, Richard H. ..... Minneapolis
† Jones, Richard N. ..... St. Cloud
Jordan, Donald V. ..... Minneapolis
† Jordan, James J. ..... Rochester
† Jordan, Kathleen B. Smith ..... Granite Falls
Jorgensen, Edward O. ..... Rochester
Jorgensen, Donald R. ..... St. Paul
Jorgensen, Harlan ..... Minneapolis
Joseph, Arnold H. ..... St. Paul
Joy, William B. ..... San Diego, CA
Joyce, John W. ..... Rochester
Judd, Allen S. ..... Minneapolis
Judd, Edward S. ..... Rochester
Judd, Walter H. ..... Washington, D.C.
† Juergens, Herman M. ..... Belle Plaine
Juergens, Manley F. ..... Stillwater
Juers, Edward H. ..... Red Wing
† Juncos, Louis I. ..... Rochester
Juntunen, Roy R. ..... Duluth
Jurdy, Mitchell ..... Minneapolis
† Just, Herman J. ..... Hastings
† Juttner, Hans-Udo ..... Rochester

K

Kaczrowski, William M. ..... Marshall
Kadesky, Harold B. ..... Minneapolis
Kaese, Werner E. ..... Rochester
Kaiser, Harold B. ..... Minneapolis
Kaiser, Milton L. ..... New Ulm
Kalb, Thomas J. ..... Minneapolis
Kallestad, Leonard L. ..... Minneapolis
Kaminski, Gregory W. ..... Redwood Falls
Kane, Dennis J. ..... Minneapolis
Kane, Morton C. ..... Minneapolis
Kane, William J. ..... Minneapolis
Kanne, Earl R. ..... Brainerd
† Kantack, Paul W. ..... Rochester
Kantar, Yale C. ..... St. Paul
Kaplan, Arnold P. ..... Minneapolis
Kaplan, David H. ..... Edina
Kaplan, J. Jacob ..... Minneapolis
Kaplan, Martin B. ..... Minneapolis
Karges, Laurel E. ..... Grand Rapids
Karish, Louis J. ..... Grand Rapids
Karleen, Conrad I. ..... Minneapolis
Karlen, Markle ..... Minneapolis

Karn, Jacob F. ..... Ortonville
Karnes, William E. ..... Rochester
Karon, Everett H. ..... St. Paul
Karon, Irvine M. ..... St. Paul
† Karsell, Philip R. ..... Rochester
Kasper, Eugene M. ..... St. Paul
Kasper, Robert E. ..... Minneapolis
† Kath, Reinhard H. ..... Merrifield
Katkov, Harold ..... Minneapolis
Katz, Beni ..... Minneapolis
Katz, Elliott S. ..... Phoenix, AZ
Katz, Harry I. ..... Minneapolis
Katz, Louis J. ..... Long Beach, CA
Kaufman, Edward J. ..... Appleton
† Kaufman, William C. ..... Appleton
Kaye, Dale R. ..... Minneapolis
Kazmier, Francis J. ..... Rochester
Kearney, R. Wynn ..... Mankato
† Kearney, R. Wynn, Jr. ..... Rochester
Kearns, Thomas P. ..... Rochester
Kegel, James F. ..... Minneapolis
Keil, Marcus A. ..... Albert Lea
† Keith, Haddow M. ..... Rochester
† Keith, Norman M. ..... Rochester
Keith, Paul J. ..... Milaca
Keithahn, Elmer E. ..... Sleepy Eye
Kelatis, Panayotis P. ..... Rochester
† Kelby, Gjert M. ..... Minneapolis
Kelley, Roger E. ..... Crosby
* Kelly, Albert C. ..... St. Paul
Kelly, Edward H. ..... St. Paul
Kelly, Helen M. ..... West St. Paul
Kelly, James H. ..... St. Cloud
Kelly, John C. ..... Minneapolis
Kelly, John F. ..... Cold Spring
Kelly, John P. ..... Minneapolis
† Kelly, John T. ..... Minneapolis
Kelly, Joseph R. ..... St. Paul
Kelly, Patrick J. ..... Rochester
Kelly, Robert T. ..... Grand Rapids
Kelly, William D. ..... Minneapolis
† Kelman, Donald B. ..... Rochester
† Kelsey, Carleton G. ..... St. Paul
Kelsey, Chauncey M. ..... St. Paul
† Kemp, Alphonse F. ..... Mankato
† Kenefick, Emmett V. ..... St. Paul
Kennedy, Byrl J. ..... Minneapolis
Kennedy, Charles C. ..... Rochester
† Kennedy, Claude C. ..... Minneapolis
† Kennedy, George L. ..... Faribault
Kenyon, Thomas J. ..... St. Paul
Kern, Eugene B. ..... Tinker AFB, OK
† Kernohan, James W. ..... Rochester
Kerr, Frederick W. L. ..... Rochester
† Kesting, Herman ..... St. Paul
Kevern, Jay L. ..... Henning
Keyes, Robert W. ..... Pipestone
† Keys, Thomas F. ..... Los Angeles, CA
Khorsand, Darius ..... Minneapolis
Kieffer, Stephen A. ..... Minneapolis
Kiely, Joseph M. ..... Rochester
Kierland, Robert R. ..... Rochester
Kiesler, Frank ..... Grand Rapids
† Kilbride, Edwin A. ..... Worthington
Kilen, Mark B. ..... Duluth
† Killean, James E. ..... Rochester
† Kim, Hyun-Hahk ..... Rochester
Kim, Mark K. ..... St. Paul
Kimmel, George C. ..... Minneapolis
Kimmel, George E. ..... Rochester
Kincaid, Owings W. ..... Rochester
Kind, Allan C. ..... Minneapolis
† King, Frances W. ..... Minnetonka
King, John E. ..... Ft. Worth, TX
Kinkade, Byron R. ..... Ada
Kinney, William N. ..... Anoka
Kiolbasa, Edward B. ..... Stillwater
† Kipfer, Robert E. ..... Rochester
† Kippen, Neil ..... Breckenridge
Kirby, Thomas J., Jr. ..... Rochester
† Kirchner, Arthur B. ..... Rochester
Kirklin, John W. ..... Birmingham, AL
Kiser, Joseph C. ..... Minneapolis
Kitzberger, Peter J. ..... New Ulm
Kjellsen, Douglas L. ..... Minneapolis
Klass, Donald W. ..... Rochester
Klefstad, Lloyd H. ..... Greenbush
† Klein, Harry ..... Duluth
Kleinsasser, Warren L. ..... St. Paul
Kleven, Lowell H. ..... Minneapolis
Knapp, James F. ..... Detroit Lakes
Knapp, Miland E. ..... Minneapolis
Knapp, Robert D., Jr. ..... Rochester
† Knight, Ralph T. ..... Minneapolis
† Knight, Ray R. ..... Minneapolis
Knip, Robert J. ..... Ortonville
Knipp, William J. ..... Brainerd
Knobloch, William H. ..... Minneapolis
Knoche, Harvey A. ..... Gaylord
Knoedler, John P. ..... Duluth
Knoll, W. V. ..... Brainerd
Knowles, William D. ..... Mankato
Knudsen, Helen L. ..... Minneapolis
Knutson, Gerhard E. ..... St. Paul
Knutson, Lewis A. ..... Spring Grove
Knutson, Robert C. ..... St. Paul
Kodres, Nina ..... St. Paul
Koelz, Thomas A. ..... St. Paul
Koenig, Robert P. ..... St. Cloud
Kohlhase, Robert E. ..... Minneapolis
Kolars, Charles P. ..... Minneapolis
† Kolars, James J. ..... Faribault
† Koller, Hermann M. ..... Minneapolis
† Koller, Louis R. ..... Minneapolis
Koller, Robert L. ..... Minneapolis
Kollmorgen, Rodger C. ..... West Point, NY
Kolp, Berton A. ..... Glenwood
† Konds, Kiyotaro ..... Rochester
Konicek, Robert G. ..... Rochester
Kooda, Jennings C. ..... Morris
Koons, William R. ..... Mahnomen
Koontz, Peter S. ..... Minneapolis
Koop, Severin H., Jr. ..... St. Cloud
Koos, Gerald W. ..... Minneapolis
† Kopp, James E. ..... Rochester
† Koppers, Lawrence E. ..... Rochester
Korchik, John P. ..... Minneapolis
Korda, Henry A. ..... Pelican Rapids
Koropchak, Nikolai ..... Minneapolis
Kosiak, Michael ..... St. Paul
Kosiak, William ..... Two Harbors
Koskela, L. E. ..... Moose Lake
Kostich, Nikola D. ..... Minneapolis
† Kostick, William R. ..... Fertile
† Kotchevar, Frank R. ..... Sun City, CA
Kottke, Frederic J. ..... Minneapolis
Kotval, Russell J. ..... Pipestone

† Koucky, Rudolph W. ..... Sagle, ID
Kovack, Freeman D. ..... Minneapolis
Koza, Donald W. ..... St. Paul
Kozak, Michael J. ..... Minneapolis
Kozel, William J. ..... Morris
Kraatz, Robert W. ..... St. Paul
Kraemer, George N. ..... Fairmont
Krafft, Walter E. ..... Minneapolis
Kragh, Lyle V. ..... Minneapolis
Kramer, Daniel W. ..... Minneapolis
Kramer, James D. ..... St. Paul
Krause, Carl W. ..... Fairmont
Kremen, Arnold J. ..... Minneapolis
Kremer, Jerome L. ..... Montevideo
† Kreuzer, Titus C. ..... New Brighton
Krezowski, Thomas K. ..... St. Paul
Krieser, Albert E. ..... Minneapolis
Krigsten, Eli J. ..... Weisbaden, Germany
† Krohn, John R. ..... Rochester
Kruger, E. Larry ..... Nashwauk
Krupp, Neal E. ..... Rochester
† Kruse, Robert L. ..... Rochester
Kruzich, Stephen J. ..... St. Cloud
Krystosek, Lee A. ..... Minneapolis
Kubista, Theodore P. ..... San Diego, CA
† Kucera, Frank J. ..... Hopkins
Kucera, Stanley T. ..... Northfield
† Kucera, William J. ..... Santa Barbara, CA
Kuehner, Marvin E. ..... Red Wing
† Kuers, Peter F. W. ..... Rochester
† Kuge, Mark T. ..... Rochester
Kugler, Alex A. ..... St. Paul
† Kuglitsch, Jack F. ..... Rochester
Kuhlmann, Lawrence B. ..... Melrose
Kuhlmann, Vernon G. ..... Alexandria
Kulstad, Oscar S. ..... Dodge Center
Kulzer, Norbert J. ..... Hastings
Kump, Warren L. ..... Minneapolis
Kuske, Albert W. ..... St. Paul
Kusske, Bradley W. ..... St. Paul
Kusske, Douglas R. ..... St. Paul
Kussy, James C. ..... Little Falls
† Kuster, Gustavo G. ..... Rochester
Kusz, Clarence V. ..... Minneapolis
Kuz, Eugene L. ..... Savage
Kvale, James N. ..... Shakopee
* Kvale, Walter F. ..... Rochester
Kvam, Lowell L. ..... St. Paul
Kvamme, Brynjulv ..... Mabel
Kvistberg, Gerald K. ..... St. Cloud
Kwako, Jerome E. ..... Duluth
Kyle, Robert A. ..... Rochester
Kyllo, John E. ..... Minneapolis
Kyllonen, Ronald R. ..... Minneapolis

L

L'Abbe, A. J. Philip ..... Duluth
L'Heureux, Philippe R. ..... Minneapolis
LaBree, John W. ..... Minneapolis
LaBree, Robert H. ..... Duluth
Lade, Roswith I. ..... St. Paul
LaFave, James W. ..... St. Paul
† LaFlamme, Georges-Henri ..... Rochester
LaFond, Edward M. ..... St. Cloud
Lagaard, Sheldon ..... Minneapolis
Laikola, Leslie A. ..... Adrian
† Lajoie, John M. ..... Minneapolis
Lake, Clifford F. ..... Rochester
LaKosky, Randall ..... Braham
Lamb, H. Douglas ..... Minneapolis
Lampert, Ronald M. ..... St. Paul
† Lamusga, David J. ..... Minnetonka
Lane, Miles I. ..... White Bear Lake
Lang, Leonard A. ..... Minneapolis
Langer, Leonard O., Jr. ..... Minneapolis
Langseth, Rodney N. ..... Duluth
Langsjoen, Ralph ..... North Mankato
Lannin, Bernard G. ..... St. Paul
Lannin, Donald R. ..... St. Paul
Lannon, James B. ..... Minneapolis
† Lantz, James P. ..... Rochester
† Lapierre, Arthur P. ..... Minneapolis
Larkin, John E. ..... St. Paul
Larrabee, Walter F., Jr. ..... Willmar
Larsen, Frank W. ..... Minneapolis
† Larsen, Russell H. ..... Lakefield
Larson, Allen K. ..... Minneapolis
Larson, Arthur K. ..... Minneapolis
Larson, Carol Ann ..... Minneapolis
Larson, Donald Marvin ..... Duluth
Larson, Donald Myren ..... Minneapolis
Larson, Donald R. ..... Crosby
Larson, Dorette W. ..... Fergus Falls
Larson, Ernest J., Jr. ..... Minneapolis
Larson, Eva Jane O. ..... St. Paul
Larson, F. Wilmer ..... Minneapolis
Larson, Gerald E. ..... Cambridge
Larson, Jerrold V. ..... St. Paul
Larson, Kenneth R. ..... Moose Lake
Larson, Lawrence M. ..... Minneapolis
Larson, Leighton W. ..... Waconia
† Larson, Leroy J. ..... Bagley
Larson, Loren J. ..... Minneapolis
Larson, Milo H. ..... St. Peter
Larson, Oliver E. H. ..... Zumbrota
Larson, Paul N. ..... Minneapolis
Larson, Richard E. ..... Minneapolis
Larson, Roger C. ..... Minneapolis
Larson, Theodore G. ..... Brainerd
Larson, Wyllis G. ..... Minneapolis
Larter, Roland R. ..... Hallock
† Laster, Charles E. ..... Rochester
† Laszewski, Franz von Zelberschwecht ..... St. Paul
Latterell, Kenneth E. ..... Duluth
Latts, Elliot M. ..... Minneapolis
Lauritzen, Herbert ..... Minneapolis
† Laventman, Jaime ..... Rochester
† LaVake, Rae T. ..... Minneapolis
Law, Harrison E. ..... Viriginia
Lawler, Kevin M. ..... St. Paul
† Lawrence, Robert B. ..... Rochester
Lawrence, Van S. ..... Minneapolis
Lawrow, John W. ..... Minneapolis
Lawson, Warren R. ..... Minneapolis
Lawton, James J., Jr. ..... Minneapolis
Layman, Thomas E. ..... St. Paul
† Leach, Clifford G. ..... St. Paul
Leach, Thomas C. ..... Babbitt
Leahy, Dennis M. ..... St. Paul
Leary, Frank J. ..... Rochester

Leavelle, Dennis E. ..... San Antonio, TX
Leavenworth, Richard O., Jr. ..... Minneapolis
† Leck, Paul C. ..... Palm Desert, CA
Lee, Gordon E. ..... Glenwood
Lee, Hubert W. ..... Brainerd
Lee, Ju Hao ..... Minneapolis
Lee, Norman J. ..... Tracy
Lee, Raymond A. ..... Rochester
Lee, Robert E. ..... Rochester
Lee, William C. ..... Hibbing
Leek, Joseph H. ..... Duluth
Leemhuis, Andrew J. ..... Minneapolis
Lees, David C. ..... Minneapolis
Lees, Jack R. ..... St. Paul
Lehman, Donald S. ..... St. Paul
Lehmann, James D. ..... Waconia
Lehrer, Alfred J., Jr. ..... Montgomery
Leick, Richard M. ..... St. Paul
Leiferman, Robert J. ..... Minneapolis
Leighton, John S. ..... Minneapolis
Leinonen, Wendla E. ..... Anoka
† Leitch, Archibald ..... South St. Paul
Leitch, Cecil M. ..... Litchfield
Lelwica, Thaddeus J. ..... Staples
Lenander, Mellvin E. L. ..... St. Peter
Lenarz, Albert J. ..... St. Cloud
Lenz, Bernard W. ..... Minneapolis
Lenz, Joseph R. ..... Morton
Lenz, Oa ..... Minneapolis
Leonard, Paul F. ..... Rochester
Leonard, Samuel ..... Minneapolis
Leonard, Stanley A. ..... St. Paul
Leonardson, Peter Y. ..... Silver Bay
† Leopard, Brand A. ..... Brownsville, TX
Leppink, Harold B. ..... Two Harbors
Leppo, N. Erkki A. ..... Duluth
Lerdahl, Kenneth ..... St. Paul
Lerner, A. Ross ..... Minneapolis
Lerner, Irving J. ..... St. Paul
Leslie, Loren R. ..... Minneapolis
Leslie, W. Robert ..... Minneapolis
Lessard, Richard J. ..... St. Paul
Lester, John W. ..... Mapleton
Lester, Malcom J., Jr. ..... Truman
Lester, Theodore H. ..... Minneapolis
Letson, Robert D. ..... Minneapolis
Leven, N. Logan ..... St. Paul
Leverenz, Carleton W. ..... St. Paul
Levine, Howard M. ..... Minneapolis
† Levitan, Alexander A. ..... Minneapolis
Levitan, Leonard H. ..... St. Paul
Levitt, George X. ..... St. Paul
Levitt, Seymour H. ..... Minneapolis
† Levy, Jonathan M. ..... Rochester
Lewis, Charles W. ..... Henning
Lewis, F. Bruce ..... Minneapolis
Lewis, Glenn M., Jr. ..... Minneapolis
Lewis, Joyce S., Jr. ..... St. Paul
*† Lick, Charles L. ..... St. Paul
Lick Louis C. ..... Minneapolis
Lick, William J. ..... St. Paul
† Lie, Jauw Tjen ..... Rochester
Liebhaber, Henia F. ..... Anoka
Lien, Richard J. ..... St. Paul
*† Liffrig, William W. ..... Red Wing
† Lightbourn, Edgar L. ..... Hastings
Lilleberg, Norbert J. ..... St. Paul
Lillehei, James P. ..... Minneapolis
Lillehei, Richard C. ..... Minneapolis
Lillie, Andrew R. ..... St. Paul
Lillie, John C. ..... Rochester
Lima, Ludvig R. ..... Montevideo
Limbeck, Donald A. ..... Minneapolis
Lindahl, Merlyn J. ..... Sherburn
Lindall, Arnold W., Jr. ..... Marine-on-St. Croix
Lindberg, Vernon L. ..... Minneapolis
Lindberg, Winston R. ..... Minneapolis
Lindblom, Alton E. ..... North Mankato
Lindeland, Arthur T. ..... Minneapolis
Lindell, Robert E. ..... St. Paul
Lindeman, Raymond J. ..... Paynesville
Lindemann, Charles E. ..... Minneapolis
Linderholm, Bruce E. ..... Minneapolis
Lindgren, Russell C. ..... Minneapolis
Lindquist, Dale C. ..... Lindstrom
Lindquist, Max F. ..... South St. Paul
Lindsay, Malcolm I., Jr. ..... Rochester
Lindseth, Easten O. ..... Excelsior
Linman, James W. ..... Rochester
Linnell, Leonard S. ..... Duluth
Linner, John H. ..... Minneapolis
Linner, Paul W. ..... Minneapolis
† Lippman, Harry H. ..... Rochester
Lippman, Hyman S. ..... St. Paul
Lipmann, Elmer W. ..... Hutchinson
Lipschultz, Oscar ..... Minneapolis
† Litin, Edward M. ..... Hopkins
Litkewitsch, Helene ..... St. Paul
Litman, Abraham B. ..... Minneapolis
† Litman, Samuel N. ..... Duluth
Litman, Thomas ..... St. Louis Park
Litzow, Thaddeus J. ..... Rochester
Lobell, Michael ..... St. Paul
Lober, Paul H. ..... Minneapolis
Locke, Murray S. ..... Minneapolis
Loeb, George L. ..... St. Cloud
Loes, Louis A. ..... St. Cloud
Lofgren, Eric P. ..... Rochester
Lofgren, Karl A. ..... Rochester
Lofsness, Stanley V. ..... Minneapolis
Lofstrom, Dennis E. ..... Brainerd
Logan, George B. ..... Rochester
Lohmann, John G. ..... Pipestone
Loken, Merle K. ..... Minneapolis
Loken, Selmer M. ..... St. Paul
Lommen, Morris ..... Austin
*† Lommen, Peter A. ..... Austin
Lommen, Peter A., Jr. ..... Austin
Long, Donlin M. ..... Minneapolis
Long, John C. ..... Chicopee Falls, MA
Longfellow, Helen W. ..... Brainerd
† Longstreth, George F. ..... Rochester
Loomis, George L. ..... Winona
Loos, Gerald D. ..... APO, New York, NY
Lorentzen, Ernest S. ..... Detroit Lakes
Lott, Frederick H. ..... Minneapolis
† Love, J. Grafton ..... Rochester
† Lovett, Beatrice R. ..... Minnetonka
Lowe, Alexander D. ..... South St. Paul
Lowe, Douglass A. ..... Minneapolis
† Lowe, Thomas A. ..... South St. Paul
Lowry, Elizabeth C. ..... Minneapolis
Lowry, Jeanette K. ..... Minneapolis
Lowry, Paul T. ..... Minneapolis
Lu, Ching-en ..... Fergus Falls
Lu, Jennie W. G. ..... Fergus Falls
Luby, Thomas H. ..... St. Cloud
† Luck, Hilda ..... Mankato

Luckey, William T. ....Minneapolis
Ludes, Bernard F. ....Rochester
Lueck, Wallace W. ....Minneapolis
Lueders, James H. ....Evansville
Lufkin, Murray W. ....St. Paul
† Lufkin, Nathaniel H. ....Minneapolis
Luh, Edwin F. ....Fergus Falls
Lukinac, Charles J. ....Minneapolis
Lukk, Olaf ....Prior Lake
Lund, George W. ....Minneapolis
Lund, J. Benjamin ....Mankato
Lund, Nancy R. ....Minneapolis
† Lund, Richard E. ....Rochester
Lund, Richard R. ....Minneapolis
† Lund, Werner J. ....Staples
*† Lundberg, Ruth I. ....St. Paul
Lundblad, Rodger R. ....Minneapolis
† Lundblad, Roy A. ....Minneapolis
Lundblad, Stanley W. ....Minneapolis
† Lundeberg, Karl R. ....Minneapolis
Lundell, Carl L. ....Granite Falls
† Lundholm, Arthur M. ....Princeton
Lundquist, Charles B. ....Minneapolis
Lundquist, Virgil J. ....Minneapolis
Lundsten, Leslie C. ....Bemidji
Lunzer, Richard G. ....St. Paul
Lynch, Francis W. ....St. Paul
Lynch, Michael F. ....Minneapolis
Lynch, Raymond P. ....St. Paul
Lynch, Richard P. ....St. Paul
† Lynde, Orrin G. ....Los Gatos, CA
Lynn, Hugh B. ....Rochester
Lyon, Fred A. ....Minneapolis
Lyon, John D. ....Hopkins
*† Lysne, Henry ....Minneapolis
Lysne, Richard B. ....Minneapolis
Lysyj, Anatol ....Minneapolis
Lyzenga, Anton G. ....Minneapolis

M

McAfee, David K. ....Willmar
McBean, James B. ....Rochester
McBride, Alexander M. ....Mankato
† McBurney, P. Louis ....Rochester
McCafferty, Charles ....St. Paul
McCaffrey, F. John ....Minneapolis
McCain, Donovan L. ....St. Paul
McCampbell, Malcolm D. ....Minneapolis
† McCann, William D. ....Rochester
McCannel, Malcolm A. ....Minneapolis
McCarten, Francis M. ....Stillwater
McCarthy, Austin M. ....Willmar
McCarthy, Charles J. ....St. Paul
† McCarthy, Donald ....Minneapolis
McClellan, Robert J. ....St. Paul
McClelland, John G. ....Virginia
McCloud, C. Naumann ....St. Paul
McCollister, Robert J. ....Minneapolis
McConahey, William M., Jr. ....Rochester
McCormick, Donald P. ....Minneapolis
† McDaniel, Orianna ....Minneapolis
† McDaniel, Samuel P. ....Lakeville
† McDonald, Thomas J. ....Rochester
† McDowell, John P. ....St. Cloud
† McDuffie, Richard W., Jr. ....Rochester
† McElfresh, Edward C. ....Rochester
McEllistrem, Edward J. ....St. Paul
McEllistrem, Gerald D. ....St. Paul
McEnaney, James E. ....Owatonna
McEwan, Alexander ....St. Paul
McFarland, Arthur H. ....Minneapolis
McGandy, Robert F. ....Minneapolis
McGee, Hugh E., Jr. ....Milledgeville, GA
McGill, Douglas B. ....Rochester
McGroarty, Brian J. ....St. Paul
McHutchison, Samuel K. ....North St. Paul
McIlrath, Donald C. ....Rochester
† McIlroy, Gary T. ....Rochester
† McInerny, Maurice W. ....Minneapolis
† McIntyre, Donald G. ....Rochester
† McIntyre, John A. ....Owatonna
† McKelvey, John L. ....St. Paul
McKelvey, John M. ....Minneapolis
McKenna, Charles H. ....Rochester
McKenna, James L. ....Minneapolis
McKenna, John J. ....Virginia
† McKenna, Jay K. ....LaJolla, CA
McKenna, Maurice J. ....Grand Rapids
McKenzie, Charles H. ....Minneapolis
McKenzie, Eva E. ....St. Paul
McKinlay, Gordon L. ....Minneapolis
McKinley, C. Richard ....Minneapolis
† McKinne, Richard A. ....Rochester
† McKinney, Frank S. ....Minneapolis
McLane, William O. ....Brainerd
McLaughlin, Byron H. ....Minneapolis
McLaughlin, Richard P. ....Minot, ND
McLeod, John A. ....Chisholm
McMahon, John E. ....Minneapolis
McNamara, John P. ....Rice
McNeil, John J. ....Minneapolis
McNeil, Maurice R. ....Glencoe
McNeil, John A. ....St. Paul
† McNutt, John R. ....Duluth
McParland, Felix A., Jr. ....Minneapolis
† McPheeters, Herman O. ....Minneapolis
McQuoid, David W. ....Excelsior
MacCarty, Collin S. ....Rochester
MacCornack, Robert L., Jr. ....South St. Paul
† MacDade, Albert D. W. ....Rochester
† MacDonald, Charles J. ....Rochester
† MacDonald, Daniel A. ....Minneapolis
MacDonald, Roger A. ....Grand Marais
† MacDonald, Vance D. ....Rochester
MacGibbon, James D. ....Minneapolis
MacKinnon, Donald C. ....Minneapolis
† Macklin, William E., Jr. ....Litchfield
MacLean, Alexander R. ....Rochester
† MacRae, Gordon C. ....Duluth
† Mach, Frank B. ....Minneapolis
Mach, John R. ....Minneapolis
Mach, Ralph F. ....Pine City
Macheledt, Neil L. ....Anoka
† Macklin, William E. ....Litchfield
Mackoff, Samuel ....Phoenix, AZ
Madland, Robert S. ....St. Paul
Madsen, Donald O. ....Minneapolis..
Maeder, Edward C. ....Minneapolis
Maeder, Edward C., Jr. ....Minneapolis
Magary, Victor J., Jr. ....South Fort Mitchell, KY
† Magath, Thomas B. ....Rochester

Magee, Timothy M. ..... Minneapolis
Magid, Gail A. ..... Santa Cruz, CA
† Magney, Fredolph H. ..... Duluth
Magnuson, Allen E. ..... Fargo, ND
Magnuson, Raymond C. ..... Combridge
Maher, Frank T. ..... Rochester
Mahle, Donald G. ..... Wabasha
† Maish, George O., Jr. ..... Rochester
Maitland, Edwin T. ..... Willmar
† Malek, Reza S. ..... Rochester
Malerich, J. Anthony ..... Cottage Grove
Malkasian, George D. ..... Rochester
Malmquist, Carl P. ..... Minneapolis
Malone, Patrick M. ..... Willmar
Mandel, Sheldon L. ..... Minneapolis
Manick, Kenneth P. ..... Minneapolis
Mankey, James C. ..... Minneapolis
Mankin, Harold T. ..... Rochester
Manlove, Charles H., Jr. ..... St. Paul
Mann, George A. ..... Minneapolis
Manoles, Elias N. ..... Minneapolis
Manolis, Deane C. ..... Minneapolis
† Manson, Roberto R. ..... Rochester
Marcoux, J. Paul ..... Rochester
† Margie, Robert P. ..... Rochester
† Marion, Dennis F. ..... Rochester
† Marik, Francis ..... Rochester
Mark, Aaron L. ..... Minneapolis
Mark, Merle S. ..... Minneapolis
Mark, Peter M. ..... Minneapolis
Marking, George H. ..... Minneapolis
Markland, Colin ..... Minneapolis
Markovitz, Jack M. ..... Minneapolis
Marshall, Clark M. ..... Crosby
Marshall, John F. ..... Pine Island
Marso, John L. ..... Mankato
Marta, John B. ..... St. Paul
Martalock, Dean L. ..... Great Lakes, IL
Marte, Egon ..... Minneapolis
Martens, Theodore G. ..... Rochester
† Martimbeau, Pierre ..... Rochester
Martin, Albert C. ..... Luverne
Martin, Doreen A. ..... Pipin, WI
Martin, Dwight L. ..... St. Paul
Martin, Frank E. ..... Minneapolis
Martin, Frederick F. ..... Bagley
Martin, George B. ..... Thief River Falls
Martin, George R. ..... Minneapolis
Martin, Gordon M. ..... Rochester
Martin, Harold R. ..... Rochester
Martin, John T. ..... Rochester
Martin, Maurice J. ..... Rochester
Martin, Webster C. ..... Duluth
* Martin, William J. ..... Rochester
Martinson, Carl J. ..... Wayzata
Martinson, Elmer J. ..... Wayzata
Martinson, Raymond M. ..... Virginia
Marvin, Joseph E. ..... Brainerd
Maryland, Daniel L. ..... Duluth
Maslansky, Robert A. ..... Minneapolis
Massee, Joseph S. ..... Minneapolis
† Masserman, Richard L. ..... Rochester
† Masson, Duncan M. ..... Rochester
† Masson, James C. ..... Rochester
Masson, James K. ..... Rochester
Mast, Frederic L. ..... Chisholm
Mastan, Peter F. ..... APO New York, NY
Mastbaum, Leonard T. ..... Minneapolis
Mateo, Guillermo ..... St. Paul
† Mathes, Peter B. ..... Rochester
Mathews, Wallace E. ..... Mankato
† Mathieson, Don R. ..... Rochester
† Mathison, Robert D. ..... Rochester
Matson, Roland W. ..... Spring Valley
Matthews, James H. ..... Minneapolis
Matthews, John A. G. ..... Minneapolis
Mattison, Percy A. ..... Winona
Mattson, Donald S. ..... Willmar
† Mattson, Roger A. ..... Minneapolis
Matus, Richard N. ..... St. Paul
Maunder, John B. ..... Minneapolis
Maus, Donald J. ..... Monticello
Maus, Philip W. ..... Dawson
† Maxeiner, Stanley R. ..... Minneapolis
Maxeiner, S. R., Jr. ..... Minneapolis
May, Horst G. ..... Duluth
May, Robert B. ..... St. Cloud
Mayberg, Donald M. ..... Minneapolis
Mayne, John G. ..... Rochester
† Mayo, Charles H., III ..... White Bear Lake
Mazzitello, William F. ..... St. Paul
Meany, Thomas J. ..... Minneapolis
Mears, Burtis J. ..... St. Paul
Mecklenburg, Fred E. ..... Minneapolis
Medelman, John P. ..... St. Paul
Medina, Ambrosio M., Jr. ..... Wayzata
Meeker, Henry C. ..... Minneapolis
Meekin, Patrick C. ..... Minneapolis
† Meinert, Albert E. ..... Winona
Meinert, John K. ..... Willmar
Melancon, Joseph F. ..... St. Paul
Melashenko, Kenneth W. ..... Karlstad
Melichar, Paul J. ..... Minneapolis
Meller, Maurice ..... Brainerd
Meller, Robert L. ..... Minneapolis
Mendesh, Anthony N. ..... Duluth
Mendiola, Ramon P., Jr. ..... Waconia
Menefee, Edward C. ..... Albert Lea
Mennis, William I. ..... Staples
Menshesa, Nicholas M. ..... Minneapolis
Mercil, C. B. ..... Mahnomen
Mercil, William F. ..... Crookston
Meredith, Donald C. ..... Mankato
Merner, Thomas B. ..... Minneapolis
† Merrick, Charlotte T. ..... St. Paul
Merrick, Robert L. ..... St. Paul
Merrick, William G. ..... Duluth
Merrill, Daniel C. ..... Minneapolis
Merrill, Robert ..... Des Moines, IA
Merritt, Wallace A. ..... Rochester
Mersy, David J. ..... Red Lake Falls
† Martens, Benny F. ..... Rochester
† Mess, Charles F. ..... Rochester
Messenheimer, Myron G. ..... Minneapolis
Metcalf, Norman ..... Princeton
Metz, Donald D. ..... Minneapolis
Meyer, Alvin J. ..... Minneapolis
Meyer, Frederick C. ..... Kenyon
Meyer, Howard J. ..... Duluth
† Meyer, Paul F. ..... Faribault
Meyer, Richard H. ..... Faribault
Meyer, Robert P. ..... Faribault
Meyer, William C. ..... Rochester
Michael, Alfred F. ..... Minneapolis
† Michael, Joseph C. ..... Pompano Beach, FL
Michaelis, Dorothy L. ..... Duluth
† Michel, Henry H. ..... Minneapolis
Michels, Roger P. ..... Willmar

† Michelson, Henry E. ..... Minneapolis
Michienzi, Leonard J. ..... St. Paul
† Mickelsen, Emma F. (Fronk) ..... Holmes Beach, FL
Mickelson, John C. ..... Los Angeles, CA
Midboe, Gilbert T. ..... Forest Lake
Middlebrook, John E. ..... Minneapolis
Midthune, Andreen S. ..... Lake Park
Midyett, F. Allan ..... Memphis, TN
Miettunen, John B. ..... Hibbing
Mijares, Wilfredo S. ..... Fairmont
Miks, George M. ..... Aurora
† Milhaupt, Emmett N. ..... Dunedin, FL
Miller, Albert G. ..... St. Paul
Miller, Gerald J. ..... Ft. Riley, KS
Miller, H. Dawes ..... Minneapolis
Miller, Harry G. ..... Virginia
Miller, Harold E. ..... Minneapolis
Miller, Herman ..... Austin
Miller, Hugo E. ..... Minneapolis
Miller, J. Carleton ..... Minneapolis
† Miller, Joe L., Jr. ..... Rochester
Miller, Linda K. ..... Winona
Miller, Roland D. ..... Rochester
Miller, Ross H. ..... Rochester
Miller, W. Eugene ..... Rochester
Miller, William P. ..... Minneapolis
Miller, Winston R. ..... St. Paul
Miller, Zondal R. ..... St. Paul
Millett, D. Keith ..... Minneapolis
Millikan, Clark H. ..... Rochester
Mills, John L. ..... Winnebago
Mills, Stephen D. ..... Rochester
Milnar, Frank J. ..... St. Paul
Milroy, Thomas W. ..... Minneapolis
Minder, John G. ..... Minneapolis
Mindrum, Gerald G. ..... Minneapolis
Minge, Raymond K. ..... Worthington
Minsky, Armen A. ..... Minneapolis
Mishek, Charles J. ..... St. Paul
Mitby, Irvin L. ..... Minneapolis
Mitchell, Berton D. ..... Minneapolis
† Mitchell, Edward C. ..... College Place, WA
Mitchell, George S. ..... St. Paul
† Mitchell, John C., III ..... Rochester
Mitchell, Mancel T. ..... Minneapolis
Mixer, Harry W. ..... Minneapolis
Mlinar, Joseph P. ..... Austin
Mock, Charles J. ..... Virginia
Moe, John H. ..... Minneapolis
† Moe, W. Wyatt ..... Minneapolis
† Moehn, John T. ..... Minneapolis
Moeller, Henry D., Jr. ..... Torrance, CA
Moen, Johannes K. ..... Minneapolis
† Moersch, Frederick P. ..... Fort Lauderdale, FL
† Moersch, Herman J. ..... Rochester
Moffitt, Emerson A. ..... Rochester
† Mokri, Bahram ..... Rochester
Moghaddam, Alaeddin ..... Minneapolis
† Molander, Herbert A. ..... St. Paul
Molenaar, Robert E. ..... Cannon Falls
Moller, Julie C. ..... Duluth
Moller, Jurgen ..... West St. Paul
Molnar, George D. ..... Rochester
Monahan, Robert H. ..... St. Paul
Mongé, James J. ..... Duluth
Monserud, Nels O. ..... Cloquet
Monson, Einer M. ..... Minneapolis
Monson, Leonard J. ..... Canby
Monson, Paul S. ..... Mound
Monson, Warren A. ..... Minneapolis
Montaniel, Necito L. ..... Crookston
† Montgomery, Hamilton ..... Rochester
Moody, David L. ..... Minneapolis
Mooney, Robert D. ..... St. Paul
† Moore, Barry B. ..... Rochester
Moore, Gordon L., II ..... Rochester
† Moore, Irvin H. ..... Eden Prairie
Moorhead, Marie ..... Minneapolis
Moos, Daniel J. ..... Minneapolis
Moral, Harvey M. ..... Minneapolis
Moran, Leo J. ..... New Brighton
Moran, Paul T. ..... St. Cloud
† Morehead, Dewey E. ..... Bodega Bay, CA
Moren, J. Adelaide ..... St. Paul
Morgan, Hugh O. ..... Amboy
Morgan, Stephen S. ..... Chesapeake, VA
Mori, Hideo ..... Grand Meadow
Moriarty, Joseph A. ..... Minneapolis
Moriarty, Joseph D. ..... Coon Rapids
† Morimoto, Allen M. ..... Rochester
Mork, A. Harold ..... Anoka
Mork, Frank E. ..... Anoka
Mork, Frank E., Jr. ..... Minneapolis
Mork, John N. ..... Worthington
Morlock, Carl G. ..... Rochester
Morrison, Charlotte J. ..... Minneapolis
Morrow, George W., Jr. ..... Rochester
† Morse, Morton P. ..... LeRoy
Morse, Roger D. ..... LeRoy
† Mortensen, Nels G. ..... St. Paul
Mortenson, Howard O. ..... Menahga
Mosby, Maurice E. ..... Long Prairie
Moss, Nyel H. ..... Minneapolis
Mosser, Donn G. ..... Minneapolis
Mossman, Philip L. ..... Minneapolis
Moulton, Keith B. ..... St. James
Mouritsen, Glenn J. ..... Fergus Falls
Mowlem, Albert ..... St. Paul
Moyer, John B. ..... Duluth
Moyer, Leonard B. ..... Minneapolis
Moyer, Richard R. ..... Hibbing
Muchow, Gene C. ..... Austin
Mueller, Donald R. ..... Grand Rapids
Mueller, James M. ..... Minneapolis
Mueller, LeRoy E. ..... Hendricks
Mueller, Rudolph B. ..... Richmond
Muesing, Mark A. ..... Tyler
Muesing, William J. ..... New Ulm
Muhm, John R. ..... Lawton, OK
† Mulcahy, John J. ..... Ann Arbor, MI
Mulder, Donald W. ..... Rochester
Mulder, Richard D. ..... Ivanhoe
Mulford, Beatrice ..... St. Paul
Mulholland, William M. ..... Minneapolis
Muller, A. Eugene ..... North St. Paul
Muller, John J. ..... Hibbing
Muller, Sigfrid A. ..... Rochester
Mulligan, Arthur M. ..... Brainerd
Mullin, Gerald T., Jr. ..... Minneapolis
Mulvahill, John E. ..... Minneapolis
Mundahl, Harold R. ..... St. Paul
Munger, James E. ..... Duluth
Munkittrick, Ronald C. ..... Minneapolis
Munneke, Lyle ..... Clara City
Munson, Martin S. ..... Moose Lake
Murn, Thomas G. ..... St. Cloud
Murphy, Jack T. ..... St. Paul

Murphy, Joseph E. ..... Marshall
Murphy, Thomas R. ..... Stillwater
† Murphy, William R. C. ..... Minneapolis
Murray, Elisabeth M. ..... Minneapolis
Murray, Robert A. ..... Hibbing
Murray, Robert A., Jr. ..... St. Cloud
Musachio, Nicholas F. ..... St. Paul
Muschenheim, Frederick ..... Minneapolis
Muske, Marvin M. ..... Minneapolis
Mussey, Mary E. ..... Rochester
Musty, Nicholas J. ..... Minneapolis
Muus, John H. ..... Staples
Myers, Jay A. ..... Minneapolis
Myers, John W. ..... Canby
Myers, Theodore P. ..... Albert Lea
Myers, Thomas T. ..... Rochester
Myers, Thomas T., III ..... Minneapolis
Myhre, James A. ..... Minneapolis
Mylrea, Murray J. ..... Burnsville
† Myre, Clifford R. ..... Paynesville

N

Nagobads, Ilgvars J. ..... Minneapolis
Nagobads, V. George ..... Minneapolis
Najarian, John S. ..... Minneapolis
Nakamura, James Y. ..... Detroit Lakes
† Nash, Eldore B. ..... Minneapolis
Nathan, Fred F. ..... Ellsworth AFB, SD
† Nauman, James C. ..... Rochester
Nauth, Bernard S. ..... Edina
Navratil, Donald R. ..... Glencoe
† Neal, Joe M. ..... Minneapolis
Nealy, Donald E. ..... Adrian
Nealy, Timothy E. ..... Blooming Prairie
Neary, Richard P. ..... Minneapolis
Neault, Roger W. ..... Rochester
Neel, Harry B. ..... Albert Lea
† Neel, H. Bryan, III ..... Rochester
Neff, Walter S. ..... Virginia
Neher, Frederick J. ..... St. Paul
Nehring, John D. ..... Chaska
Neils, Vernon E. ..... St. Cloud
Neira, Edward H. ..... St. Paul
Nelimark, Donald R. ..... Virginia
† Nelson, Audrey M. ..... Rochester
Nelson, Bernette G. ..... Ely
† Nelson, Bernice A. ..... New Brighton
Nelson, C. Barton ..... Minneapolis
Nelson, Carleton A. ..... Minneapolis
Nelson, Clayton E. J. ..... Albert Lea
† Nelson, David J. ..... St. Paul
† Nelson, David W. ..... Minneapolis
Nelson, Delbert R. ..... St. Paul
Nelson, Edward N. ..... Minneapolis
Nelson, Evan L., Jr. ..... Minneapolis
Nelson, George E. ..... Minneapolis
Nelson, Glen D. ..... Minneapolis
Nelson, Glenn E. ..... Redwood Falls
Nelson, Gunard A. ..... Minneapolis
† Nelson, Harvey ..... Deerfield Beach, FL
† Nelson, Henry E. ..... Crookston
Nelson, Lloyd S. ..... Mineapolis
Nelson, Loren E. ..... St. Paul
Nelson, Louis A. ..... St. Paul
Nelson, Luther A. ..... Rush City
Nelson, Maxine O. ..... Minneapolis
Nelson, Maynard C. ..... Minneapolis
Nelson, O. L. Norman ..... Minneapolis
Nelson, Robert H. ..... Benson
Nelson, Robert P. ..... St. Paul
Nelson, Ronald J. ..... St. Paul
Nelson, Roy A. ..... Fergus Falls
Nelson, Wallace I. ..... Minneapolis
Nerenberg, Sidney ..... Minneapolis
Neshiem, Martin O. ..... Albert Lea
Ness, Duane E. ..... Wadena
Ness, Richard A. ..... Fergus Falls
Nesse, James A. ..... Austin
Nesset, David G. ..... Rochester
Nesset, Lawren B. ..... Minneapolis
Nesset, William D. ..... Minneapolis
Nesvacil, Leon ..... St. Paul
Neumann, Roland F. ..... Minneapolis
Neumeister, Charles A. ..... Minneapolis
Neuwirth, Gerardo D. ..... Minneapolis
Niazi, Suad A. ..... Granite Falls
Nicholas, S. Scott, Jr. ..... Minneapolis
† Nicholas, Karl R. K. ..... Rochester
† Nichols, Charles P. ..... Rochester
Nichols, Donald R. ..... Rochester
Nichols, Thomas O. ..... St. Paul
Nicholson, Richard W. ..... Fergus Falls
Nickerson, John R. ..... Faribault
Nickerson, Neil D. ..... Fairmont
Nicollette, Charles C. ..... Minneapolis
Nielsen, David J. ..... Minneapolis
Nietfeld, Aloys B. ..... Sauk Centre
Nilsen, John A. ..... Minneapolis
† Nimlos, Kenneth O. ..... St. Paul
† Nimlos, Lenore O. ..... St. Paul
Nisius, George F. ..... Duluth
† Niven, Robert G. ..... Rochester
Nisswandt, Albert L. ..... Duluth
Nixon, James B. ..... Crosby
Nixon, Rodney T. H. ..... Grand Rapids
Nobrega, Fred T. ..... Rochester
† Nolan, Declan R. ..... Rochester
Nolan, Robert K. ..... Minneapolis
Nolan, William ..... Litchfield
Nollet, Donald J. ..... Hibbing
Noran, Harold H. ..... Minneapolis
† Norberg, Carl E. ..... Los Altos, CA
Norberg, William J. ..... Detroit Lakes
Nord, Robert E. ..... Minneapolis
† Nordlie, Paul E. ..... Minneapolis
Nordlund, Mildred E. ..... Carmichael, CA
Nordman, Willard F. ..... Mora
Noren, George R. ..... Minneapolis
Norman, David D. ..... St. Paul
Norman, Franklin C. ..... Minneapolis
Norman, Mark L., Jr. ..... Minneapolis
Normann, Stephen T. ..... Waseca
Norquist, Joseph L. ..... St. Paul
Norris, John C. ..... Mankato
Norval, Mildred A. ..... Minneapolis
Nuebel, Charles J. ..... Long Beach, CA
† Nuessle, Walter G. ..... Springfield
Nuessle, William F. ..... Minneapolis
† Nuss, Donald ..... Rochester
Nydahl, Bruce C. ..... Minneapolis
Nydahl, Malvin J. ..... Minneapolis
† Nye, Lillian L. ..... St. Paul
Nygren, William T. ..... Braham
Nywall, Dean D. ..... Slayton

O

O'Brien, Bruce J. ....Minneapolis
O'Brien, Gerald R. ....Minneapolis
O'Brien, John C. ....St. Paul
O'Brien, Louis T. ....Breckenridge
O'Brien, William A. ....Minneapolis
† O'Donnell, James E. ....Minneapolis
O'Duffy, John D. ....Rochester
O'Kane, Thomas W. ....St. Paul
O'Keefe, James P. ....St. Cloud
O'Malley, Valentine ....St. Paul
O'Neil, Bernerd L. ....Minneapolis
O'Neill, John C. ....Duluth
O'Neill, Nial C. ....St. Paul
O'Phelan, E. Harvey ....Minneapolis
† O'Reilley, Bernard E. ....Sun City, AZ
O'Rourke, William J. ....Austin
Obetz, Samuel W. ....Rochester
*† Ochsner, Clarence G. ....Santa Barbara, CA
Ockuly, Orville E. ....St. Paul
Odland, Donald M. ....Luverne
Odland, Mark E. ....Detroit Lakes
Odland, Olin M. ....Marshall
† Odyniec, Norman A. ....Rochester
Oeljen, Siegfried C. ....Waseca
Officer, Charles D. ....Burnsville
† Ogden, Warner ....River Falls, WI
† Ohage, Justus ....St. Paul
Ohmann, Ronald J. ....Minneapolis
Olavs, Olga ....Minneapolis
Olds, George H. ....New Richland
Olfelt, Paul C. ....Minneapolis
Olinger, John N. ....St. Cloud
Olmanson, Edmund G. ....St. Peter
Olmanson, M. Donald ....St. Peter
Olmanson, Vern C. ....St. Peter
Olsen, Arthur M. ....Rochester
† Olsen, E. George ....Minnetonka
Olsen, Jay R. ....Minneapolis
Olsen, Ralph L. ....St. Paul
Olson, Albert J. ....Owatonna
Olson, Alton C. ....Minneapolis
Olson, Barbara F. ....Minneapolis
Olson, C. Kent ....Minneapolis
Olson, Carl J. ....Minneapolis
Olson, Detlof M. ....Minneapolis
Olson, Duane C. ....Minneapolis
Olson, Frances P. ....Fergus Falls
Olson, Grant E. ....West Concord
Olson, Gregory M. ....Litchfield
Olson, Hardin E. ....Minneapolis
Olson, Lillian A. ....Ah-Gwah-Ching
† Olson, Neal R. ....Rochester
† Olson, Olof A. ....Minneapolis
Olson, Philip A. ....Minneapolis
Olson, Richard E. ....Chaska
Olson, Richard T. ....Virginia
Olson, Robert A. ....Minneapolis
Olson, Robert E. ....Minneapolis
Olson, Robert T. ....Canby
Olson, Robert W. ....Minneapolis
Olson, Rolland A. ....Wayzata
Onofrio, Burton M. ....Rochester
† Onsgard, L. Kenneth ....St. Petersburg, FL
Onstad, Gerald R. ....San Francisco, CA
† Opgrande, John D. ....Rochester
Opheim, Richard H. ....Minneapolis
Opitz, Joachim L. ....Rochester
† Oppegaard, C. L. ....Scottsdale, AZ
Oppen, E. Gerhard ....Minneapolis
Oppen, Melvin G. ....Minnetonka
Opsahl, Lawrence J. ....Willmar
Opstad, Earl T. ....Minneapolis
Orandi, Ahmad ....Fergus Falls
Orandi, Mehdi ....Fergus Falls
Orbuch, Martin W. ....Minneapolis
Orkin, Milton ....Minneapolis
Orn, Duane L. ....Minneapolis
Orr, Burton A. ....Faribault
*† Oschsner, Clarence G. ....Santa Barbara, CA
Osekowsky, Henry J. ....St. Paul
Osmundson, Philip J. ....Rochester
Osterberg, Kenneth A. ....Minneapolis
† Ostergaard, Erling ....Elbow Lake
*† Ostergren, Edward W. ....St. Paul
Ostrov, Charles S. ....Minneapolis
Ott, Eugene C. ....Minneapolis
Ouellette, Alfred J. ....St. Paul
Ourada, Anthony L. ....Buffalo
Overby, Philip G. ....Minneapolis
Overgaard, Peter H., Jr. ....Lindstrom
Owen, Charles A., Jr. ....Rochester
Owen, Richard R. ....Minneapolis
Owens, Ben P. ....Hibbing
Owens, Frederick M. ....St. Paul
Owens, William A. ....Montevideo
† Oxman, Herbert A. ....Rochester

P

Paal, Dwain J. ....Minneapolis
Paciotti, Vincent J. ....Hibbing
† Page, Raymond L. ....St. Paul
† Pairolero, Peter C. ....Rochester
Paisner, Hyman M. ....Minneapolis
Palattao, Agustin D., Jr. ....Waconia
Palen, Benjamin J. ....Scottsdale, AZ
Palm, E. Theodore ....Minneapolis
Palm, Neil M. ....St. Paul
Palmer, Clinton F. ....Albert Lea
Palmer, Harry A. ....Blackduck
Palumbo, Pasquale J. ....Rochester
Panning, Wayne P. ....Marshall
Paparella, Michael M. ....Minneapolis
Papermaster, Ralph ....Minneapolis
Papermaster, Theodore C. ....Wayzata
† Pappalardo, Frank J. ....Rochester
† Paradis, Gaston R. ....Rochester
† Park, Moon Soo ....Rochester
Park, Wilford E. ....Minneapolis
Parker, Robert L. ....Rochester
Parker, Warren E. ....Sebeka
Parker, Wilbert H. ....Chisholm
† Parkhill, Edith M. ....Rochester
Parod, John D. ....Minneapolis
Parra, Samuel ....Crookston

Parrott, John C. ..... Minneapolis
† Parry, Rodney R. ..... Rochester
Parson, E. Irvine ..... Duluth
Parsons, R. A. ..... St. James
Parsons, Ralph L. ..... Trimont
Pasek, Antone W. ..... Cloquet
Passmore, James A. ..... Ft. Sam Houston, TX
Patch, Orien B. ..... Duluth
† Patrick, Donald L. ..... Rochester
Pattee, James J. ..... Minneapolis
Patterson, Hugh D. ..... Slayton
Patterson, Paul G. ..... Minneapolis
Paule, William J. ..... Minneapolis
Paulson, Elmer C. ..... St. Paul
Paulson, Wallace J. ..... St. Paul
Payne, Richard E. ..... Virginia
Payne, W. Spencer ..... Rochester
Peake, Janna Z. ..... St. Paul
Pearson, Bror F. ..... Shakopee
† Pearson, Fritz R. ..... St. Paul
Pearson, Harris L. ..... Bagley
Pearson, Malcolm M. ..... St. Paul
† Pease, Gertrude L. ..... Rochester
† Pedersen, Arthur H. ..... St. Paul
Pedersen, Robert L. ..... Brainerd
* Pedersen, Roy C. ..... Duluth
Peikert, Carl F. ..... Forest Lake
Peiper, Warren S. ..... Minneapolis
Pelletier, Rene W. ..... St. Paul
Peluso, Charles R. ..... Minneapolis
Pelzl, Charles R. ..... Pine River
Penk, Engward L. ..... Springfield
Penn, George E. ..... Mankato
Pennington, Mary ..... Minneapolis
Peper, Martin C. ..... Minneapolis
Perkins, Douglass E. ..... Alexandria
Perlman, Everett C. ..... Minneapolis
Perlman, Herschel L. ..... St. Louis Park
Perry, Harold O. ..... Rochester
Perry, John F., Jr. ..... St. Paul
Perry, Lawrence B. ..... Rochester
Person, Duane F. ..... Virginia
Pesonen, Clifford ..... Austin
Peteler, Jennings, C. L. ..... Minneapolis
Peters, Gustavus A. ..... Rochester
Petersen, Byron D. ..... Minneapolis
Petersen, Deane A. ..... Wayzata
Petersen, Donald H. ..... Willmar
Petersen, Glenn L. ..... Minneapolis
† Petersen, Magnus C. ..... Rochester
Petersen, Robert T. ..... St. Cloud
Petersen, William E. ..... Minneapolis
Peterson, Alvin C. ..... Mora
Peterson, Charles A. ..... Minneapolis
† Peterson, Charles A. ..... Rochester
Peterson, Charles R. ..... Minneapolis
Peterson, Donald H. ..... St. Paul
Peterson, Edward A. ..... St. Paul
Peterson, Edward N. ..... Virginia
Peterson, Hamlet A. ..... Rochester
Peterson, Harold O. ..... Minneapolis
† Peterson, Joel L. E. ..... St. Paul
Peterson, John A. ..... Minneapolis
Peterson, John H. ..... Duluth
Peterson, John O. H. ..... Hastings
Peterson, John R. ..... Rushford
Peterson, Kenneth A. ..... Marshall
Peterson, Kenneth H. ..... Hutchinson
Peterson, Lowell F. A. ..... Rochester
Peterson, Oliver H., Jr. ..... Minneapolis
Peterson, Palmer A. ..... Minneapolis
Peterson, Rodney H. ..... Minneapolis
Peterson, Roy A. ..... Vesta
Peterson, Roy L. ..... White Bear Lake
Peterson, Stanley C. ..... Austin
Peterson, Theodore A. ..... Minneapolis
*† Peterson, Willard C., Sr. ..... Minneapolis
Peterson, Willard C., Jr. ..... Minneapolis
Peterson, Willard E. ..... Willmar
Petit, Julien V. ..... Minneapolis
† Petit, Leon J. ..... Minneapolis
Petitt, Robert M. ..... Rochester
Petraborg, Harvey T. ..... Aitkin
Pettersen, George R. ..... Aitkin
† Petty, Roy W. ..... Rochester
Pewters, John T. ..... Minneapolis
Peyla, Thomas L. ..... Rochester
Pfohl, Richard A. ..... Minneapolis
Phares, Otto C. ..... St. Cloud
† Phelps, Kenneth A. ..... Palo Alto, CA
Phelps, Robert D. ..... Minneapolis
Phibbs, Clifford M., Jr. ..... Minneapolis
Phillips, Leonard ..... St. Paul
Philp, David R. ..... Watertown
† Pien, Francis D. ..... Rochester
Pierce, Robert B. ..... Heron Lake
Pierre, Robert V. ..... Rochester
Pierson, Roy F. ..... Slayton
Pietan, Jerold H. ..... Chisholm
† Pikler, George M. ..... Rochester
Pilling, Loran F. ..... Minneapolis
Pilney, Frank T. ..... St. Paul
Pincus, Mitchell ..... Minneapolis
Pinell, Octavio C. ..... Minneapolis
Pinsonneault, W. A. ..... Roseau
*† Piper, William A. ..... Mountain Lake
Pistulka, Rolland D ..... Chaska
Pitcher, Arlo L. ..... St. James
Pivac, Dragojla (Popovich) ..... Milwaukee, WI
Pizarro, Remi L. ..... Minneapolis
Plasha, Matthew K. ..... Coon Rapids
Plass, Herbert F. R. ..... Minneapolis
Pleissner, Karl W. ..... Minneapolis
† Pliam, Michael B. ..... Rochester
Plimpton, Nathan C. ..... Minneapolis
Plotke, Harry L. ..... St. Paul
Plucker, Milton W. ..... Worthington
† Plummer, Alan L. ..... Rochester
† Plummer, Leo J. ..... Rochester
Pluth, James R. ..... Rochester
Pohl, John F. ..... Minneapolis
† Poland, Jerome D. ..... Minneapolis
Polesky, Herbert F. ..... Minneapolis
Poley, Brooks J. ..... Minneapolis
Pollak, Kurt ..... Minneapolis
Pollard, William S. ..... Duluth
Polley, Howard F. ..... Rochester
Pollman, Stanley E. ..... Naha, Okinawa
Pollock, Anthony J. ..... Minneapolis
Polski, Paul G. ..... South St. Paul
† Polzak, James A. ..... Roseville
Pone, John J. ..... Minneapolis
Ponterio, James E. ..... Shakopee
† Pool, T. Lloyd ..... Rochester
Poole, James R. ..... North St. Paul
Popadiuk, Peter ..... Minneapolis
Pope, David A. ..... Janesville
Popoff, Russel G. ..... Graceville

Popowich, John G. ..... Minneapolis
† Poppe, Frederick H. ..... Miami, FL
Poppie, Robert W. ..... Brainerd
† Port, Friedrich K. ..... Rochester
Post, Edmund A. ..... St. Paul
Poston, Lawrence M. ..... Caledonia
Potter, Robert B. ..... Minneapolis
† Powell, David F. ..... Rochester
Power, John E. ..... Duluth
Powers, Robert L. ..... St. Paul
Pozuelo, Utanda, Jose ..... Rochester
† Pratt, Fred J. ..... Minneapolis
Pratt, Joseph H., Jr. ..... Rochester
Prentice, James A. ..... Rochester
Prentice, Walter B. ..... St. Paul
Prem, Konald A. ..... Minneapolis
Preston, Frank S., Jr. ..... Minneapolis
Price, William E. ..... Minneapolis
Prickman, William E. ..... Minneapolis
Priest, Robert E. ..... Minneapolis
† Priestley, James T. ..... Rochester
*† Prim, Joseph A. ..... Minneapolis
† Pritchard, Douglas J. ..... Rochester
Prlina, Issac M. ..... Virginia
Proeschel, Ray K. ..... Willmar
Proshek, Lumir C. ..... Minneapolis
Proud, Harry S. ..... St. Paul
Provence, Cecil L. ..... Waconia
Pruitt, Raymond D. ..... Rochester
Pugh, David G. ..... Rochester
Pulido, Ernesto D. ..... Fergus Falls
Pumala, Erven E. ..... Warren
Purdie, James L. ..... Forest Lake
Purnell, Don C. ..... Rochester
Purves, G. Harland ..... Buffalo
Puumala, Barbara M. ..... Cloquet
Puumala, Reino H. ..... Cloquet
Puumala, Ricard R. ..... Cloquet

Q

Quattlebaum, Frank W. ..... St. Paul
Quello, Robert O. B. ..... Minneapolis
Quiggle, Arthur B. ..... Minneapolis
Quist, Henry W., Jr. ..... Minneapolis

R

Raab, David E. ..... Minneapolis
Raaen, Olaf J. ..... St. Paul
Rabcevich, Anatole ..... St. Paul
Racer, Harley J. ..... Minneapolis
Radke, Robert L. ..... Milan
Raetz, Sylvester J. ..... Maple Lake
† Rahimi, Abbas ..... Rochester
Raich, John J. ..... Minneapolis
Raile, Richard B. ..... Minneapolis
† Raimundo, Hugo Sa ..... Rochester
Ralph, James R. ..... St. Paul
Ralston, Donald E. ..... Rochester
Ramlow, Ralph M. ..... West St. Paul
† Ramsey, Walter R. ..... St. Paul
Randall, David A. ..... Minneapolis
Randall, Raymond V. ..... Rochester
Ransom, H. Robert ..... Osseo
Ratelle, Alexander E. ..... Minneapolis
Raths, Otto N., Jr. ..... St. Paul
Ravits, Harold G. ..... St. Paul
Rayner, Ralph R. ..... Red Wing
Rea, Charles E. ..... St. Paul
Reardon, Andrew E. ..... Duluth
Recht, Thomas M. ..... Minneapolis
† Reckles, Lawrence N. ..... Rochester
Redleaf, Paul D. ..... St. Paul
Reeber, Erick ..... Bagley
Reece, Richard L. ..... Minneapolis
Reed, Henry H. ..... Duluth
Reed, John H., Jr. ..... Minneapolis
Reed, Paul ..... Virginia
Reed, Sheldon C. ..... Minneapolis
Reese, David F. ..... Rochester
Reeves, Bradford F. ..... Fort Campbell, KY
Reff, Alan R. ..... Crookston
Regan, John J. ..... Minneapolis
*† Regnier, Edward A. ..... Minneapolis
Rehmann, Ronald E. ..... Coon Rapids
Reichel, Samuel M. ..... Minneapolis
Reichelderfer, Charles F. ..... Staples
Reichelt, Leland G. ..... Wadena
† Reick, Robert R. ..... Rochester
Reid, Howard C. ..... Bemidji
Reid, James W. ..... South St. Paul
Reif, Harold A. ..... Minneapolis
Reif, Robert W. ..... White Bear Lake
Reiley, Richard E. ..... Minneapolis
Reilly, William F., Jr. ..... Davis-Monthan AFB, AZ
† Reimer, Marvin S. ..... Rochester
Reiners, Gary L. ..... Cambridge
Reinhardt, James H. ..... Alexandria
Reinhart, Richard O. ..... Minneapolis
Reisdorf, George E. ..... Minneapolis
Reiser, Milton P. ..... Minneapolis
† Reitemeier, Richard J. ..... Rochester
† Reller, Carl R., Jr. ..... Minneapolis
ReMine, William H., Jr. ..... Rochester
Remole, William D. ..... Minneapolis
Remsberg, John R. S. ..... Minneapolis
† Replogle, William H. ..... Eugene, OR
Resch, Joseph A. ..... Minneapolis
Restall, Charles J. ..... Rochester
Reynolds, Dermot F. ..... Hibbing
Reynolds, James C. ..... San Antonio, TX
Reynolds, James F. ..... Minneapolis
Rhodes, Clinton E. ..... Willmar
Rholl, Arnold O. ..... Minneapolis
Rhoton, Albert L. ..... Rochester
Rice, Carl O. ..... Minneapolis
Rice, Edwin G. ..... Minneapolis
Rice, Frank B. ..... St. Paul
Rice, Fred A. ..... Minneapolis
Rice, Hagbart G. ..... Moorhead
Rice, William H. ..... St. Cloud
† Richards, William B. ..... St. Cloud
Richardson, Edward J. ..... St. Paul
Richardson, Robert J. ..... Minneapolis

† Richdorf, Lawrence F. ..... Minneapolis
Richter, David J. ..... Virginia
Richter, Paul H. ..... Fergus Falls
Rick, Paul F. W. ..... St. Paul
Rierson, Phillip A. ..... Minneapolis
Rieschl, Elizabeth K. ..... Jordan
Riggs, B. Lawrence ..... Rochester
Riley, John D. ..... Minneapolis
Rimas, Matthew J. ..... Comfrey
Ringhofer, Lawrence ..... New Ulm
† Ringle, Otto F. ..... Walker
Rinkey, Eugene ..... St. Paul
Riordan, Elsie M. ..... Minneapolis
Ripple, Rudolph J. ..... St. Paul
† Ripple, Rudolph J., Jr. ..... Minneapolis
Risch, Ronald E. ..... Minneapolis
Risser, Alden F. ..... Stewartville
Ristic, Miodrag ..... Cambridge
Ritchie, Donald A. ..... St. Cloud
† Ritt, Albert E. ..... St. Paul
Ritter, Donald G. ..... Rochester
Rivan, Robert J. ..... Rochester
Rivers, Thomas A. ..... Colorado Springs, CO
Rizer, Dean K. ..... Minneapolis
Roach, Charles A. ..... St. Paul
Roach, Donald E. ..... St. Paul
† Robb, Edwin F. ..... Minneapolis
Robbins, Owen F. ..... Minneapolis
Roberts, Byron H. ..... Minneapolis
Roberts, George A. ..... Austin
Roberts, Lewis J. ..... Minneapolis
† Roberts, Oliver W. ..... Owatonna
Robertson, Dennis M. ..... Rochester
† Robertson, Paul A. ..... Austin
† Robertson, Robert C. ..... Rochester
Robinson, Cortland O. ..... Minneapolis
Robinson, William W. ..... Agana, Guam
Robnik, Spencer L. ..... Willmar
Rock, William H. ..... Anoka
Rocknem, Robert E. ..... Minneapolis
Rockwell, Curtiss V. ..... Minneapolis
Rockwood, Philo H. ..... Fergus Falls
† Rodarte, Joe R. ..... Rochester
Rodgers, Richard S. ..... Minneapolis
† Roehlke, Arthur B. ..... Elk River
Roemer, Henry J. ..... Winona
Rogers, Charles W. ..... Winona
Rogin, Norton ..... Minneapolis
† Roholt, Christian ..... McIntosh
Roholt, Hartvig B. ..... Bemidji
† Rohrer, Christian A. ..... Madison Lake
Rolig, David H. ..... West St. Paul
Rollie, Orris O. ..... St. Paul
Rollins, Pat ..... Minnetonka
Rome, Howard P. ..... Rochester
Romero, Jose B. ..... St. Paul
Romness, Kenneth B. ..... Mound
Rooke, F. Douglas ..... Rochester
Rorem, Joseph A. ..... Appleton
Rose, Cordt ..... Albert Lea
† Rosenbaum, Alan H. ..... Rochester
Rosenbaum, David L. ..... Minneapolis
† Rosenbaum, Robert A. ..... Rochester
Rosendahl, Frederick G. ..... Minneapolis
† Rosenfield, Abraham B. ..... Minneapolis
† Rosenquist, Rudolph J. ..... Minneapolis
Rosenow, Edward C., III ..... Rochester
Rosenow, John H. ..... Minneapolis
Rosenstein, Hanan J. ..... Minneapolis
† Rosenthal, Robert ..... St. Paul
† Rosenwald, Reuben M. ..... Anoka
Rosevear, John W. ..... Minneapolis
Ross, James V., Jr. ..... Rochester
Rossberg, Raymond A. ..... Morris
Rossen, Ralph X. ..... Minneapolis
Rossing, Robert G. ..... Brooks AFB, TX
Rotenberg, Robert J. ..... Minneapolis
Rotenberg, Samuel ..... Beverly Hills, CA
Roth, Albert H. ..... Deer River
Roth, Charles W. ..... Red Wing
Roth, Frederick D. ..... Mankato
Roth, George C. ..... St. Paul
Rothnem, Morris S. ..... Minneapolis
† Roubinian, Jirayr R. ..... Rochester
Roust, Henry A. ..... Montevideo
Rovelstad, Randolph A. ..... Rochester
Rowe, Clarence J., Jr. ..... St. Paul
Rowe, Richard G. ..... Duluth
† Rowles, Everett C. ..... Laguna Hills, CA
Roy, Philemon C. ..... St. Paul
Roy, Paul H. J. ..... Quebec, Canada
Rozeboom, Paul E. ..... Mankato
Rozycki, Anthony T. ..... St. Cloud
Rubin, Jacob S. ..... Crookston
Rubin, Manly ..... Minneapolis
Ruchie, Warren H. ..... Willmar
† Rucker, Charles W. ..... Rochester
Rucker, Thomas K. ..... Minneapolis
† Rucker, William H. ..... Minneapolis
† Rud, Norman E. ..... Edina
Rud, Paul D. ..... Luverne
Rudie, Peter S. ..... Duluth
Rudie, William D. ..... Duluth
† Rue, David S. ..... Rochester
Ruggles, George M. ..... Forest Lake
† Ruhberg, George N. ..... Santa Barbara, CA
Ruhe, Albert H. ..... Willmar
Ruiz, Ernest ..... Minneapolis
Rukavina, John G. ..... St. Paul
† Rumpf, Carl W. ..... Faribault
Runquist, John M. ..... Duluth
Runquist, Richard K. ..... Cambridge
Rushay, Arthur J. ..... White Bear Lake
Rushton, Joseph G. ..... Rochester
Russ, Homer H. ..... Blue Earth
† Russ, Homer H., Jr. ..... Rochester
† Russell, Rex D. ..... Rochester
Russeth, Arthur N. ..... Minneapolis
Rusten, Elmer M. ..... Minneapolis
Rusterholz, Alan P. ..... St. Paul
Ruth, Bradley R. ..... Duluth
Rutledge, John B. ..... Detroit Lakes
† Rutledge, Lloyd H. ..... Detroit Lakes
Ryan, Edward A. ..... Duluth
† Ryan, John J. ..... St. Paul
Ryan, Joseph M. ..... St. Paul
† Ryan, William E. ..... Rochester
Rydberg, John S. ..... Minneapolis
* Rydburg, Wayne C. ..... Minneapolis
† Rydell, Ralph E. ..... Rochester
Ryding, Vincent ..... Ames, IA
Rydland, Arne D. ..... Minneapolis
Rygh, Harold N. ..... Atwater
† Rynearson, Edward H. ..... Rochester
Rysgaard, George N. ..... Northfield

S

Sach-Rowitz, Alvan ..... Moose Lake
Sadd, Milton ..... Willmar
Saffert, Cornelius A. ..... New Ulm
St. Cyr, Harry M. ..... Minneapolis
St. Cyr, Kenneth J. ..... Minneapolis
† Salanga, Virgilo D. ..... Rochester
Salassa, Robert M. ..... Rochester
Salchert, John J. ..... Minneapolis
Salk, Richard J. ..... Albany
Saliterman, Bernard I. ..... Minneapolis
Saloum, Lucille M. ..... Duluth
Salovich, Edward L. ..... Minneapolis
Salovich, Elmer R. ..... Minneapolis
† Salter, Reginald A. ..... Virginia
Salter, Wilson M. ..... Willmar
Sams, W. Mitchell, Jr. ..... Rochester
Samuel, Visuvasam N. ..... Rochester
Sanchez, Jose S. ..... Edina
Sand, Richard E. ..... St. Paul
Sandeen, Richard M. ..... Buffalo
Sandell, Samuel T. ..... Duluth
Sander, Frank V., Jr. ..... Rochester
Sander, John L. ..... Red Wing
Sanderson, David J. ..... Fergus Falls
Sanderson, David R. ..... Rochester
Sandkamp, Virgil A. ..... South St. Paul
Sandok, Burton A. ..... Rochester
Sandt, Karl E. ..... La Jolla, CA
† Sanfelippo, Peter M. ..... Rochester
Sanfilippo, Sylvester J. ..... Minneapolis
Sanford, John B. ..... Duluth
Sanford, Raymond A. ..... Mankato
Sargent, John H. ..... St. Paul
Sartor, Richard ..... Minneapolis
† Satava, Richard M. ..... Rochester
Sather, Edgar L. ..... Fosston
Sather, George A. ..... Fosston
Sather, Richard N. ..... Fosston
† Sather, R. Alan ..... Oklahoma City, OK
Sather, Russell O. ..... Crookston
Sauer, Jean C. ..... Fort Snelling
Sauer, Robert L. ..... Preston
Sauer, William G. ..... Rochester
Savelkoul, Gene R. ..... Belgrade
Savett, Laurence A. ..... St. Paul
Sawtell, Robert R. ..... Rochester
Sawyer, Glenn T. ..... Minneapolis
Sax, Milton H. ..... Duluth
Sax, Simon G. ..... Duluth
Saxena, Krishna M. ..... St. Paul
Saxman, Gertrude E. O. ..... Ulen
Sayre, George P. ..... Rochester
Sayther, Keith D. ..... Minneapolis
Sborov, Abe M. ..... Minneapolis
Scallen, Raymond W. ..... Minneapolis
† Scallen, Edward S. ..... Rochester
Scanlan, Patrick J. ..... Minneapolis
Scanlon, Hugh A. ..... Little Falls
Scanlon, Paul W. ..... Rochester
Schaar, Frances E. ..... Minneapolis
† Schade, Frederick L. ..... Santa Cruz, CA
† Schaefer, Joseph F. ..... Sun City, AZ
Schaefer, Wesley G. ..... Minneapolis
Schafer, Charles F. ..... Winona
Schaffhausen, George E. ..... St. Paul
Schaffhausen, Irwin F. ..... Minneapolis
Schaffhausen, Mildred ..... Minneapolis
Schamber, Walter F. ..... St. Cloud
Scheidel, Alois M. ..... Mankato
Scherck, Jerome J. ..... St. Paul
Scherer, L. Raymond ..... Minneapolis
Scherling, Sidney S. ..... Minneapolis
Scheuneman, Allen F. ..... Thief River Falls
Schiele, Burtrum C. ..... Minneapolis
Schimelpfenig, George T. ..... Chaska
Schirber, Martin J. ..... Grand Rapids
Schirger, Alexander ..... Rochester
Schissel, Gregory A. ..... Minneapolis
Schissel, Richard C. ..... Minneapolis
Schloff, Ivan ..... St. Paul
Schloff, Leonard D. ..... St. Paul
Schmid, John F. ..... Duluth
† Schmidt, Hilmar R. ..... Winona
Schmidt, Paul G. ..... Granite Falls
Schmidt, Ruben F. ..... Alden
Schmidt, W. Robert ..... Minneapolis
Schmidtke, Reinhardt L. ..... St. Paul
† Schmitt, S. C. ..... Fallbrook, CA
Schmitz, Anthony A. ..... Mankato
Schmitz, Everett J. ..... St. Cloud
Schnabel, Norma B. ..... Crookston
Schnabel, Robert F. ..... Crookston
Schneck, Jack I. ..... Minneapolis
Schnell, Frederick S. ..... Litchfield
† Schnur, Paul L. ..... Rochester
*† Schoch, Robert B. J. ..... St. Paul
Schochet, H. Laurence ..... St. Paul
† Schoen, Roland F. ..... San Francisco, CA
† Schoenberg, Bruce S. ..... Rochester
Schoenberger, P. B. ..... Perham
Schoening, Herbert A. ..... Minneapolis
Schoenwetter, William F. ..... Minneapolis
Scholz, Donald A. ..... Rochester
† Schons, Edward ..... Minnetonka Beach
Schossow, George W. ..... White Bear Lake
Schottler, Jerry L. ..... Minneapolis
Schottler, Max E. ..... Minneapolis
Schotzko, John R. ..... Blue Earth
Schrader, Wayne H. ..... St. Paul
Schrantz, Robert D. ..... Rochester
Schroeckenstein, Hugo F. ..... St. Paul
Schroeder, Albert J. ..... Minneapolis
Schroeder, Glenn E. ..... Red Wing
† Schroeder, James G. ..... Rochester
Schroeppel, Roger ..... Tracy
Schulberg, Verne A. ..... Minneapolis
Schultz, Alan K. ..... Minneapolis
Schultz, Alvin L. ..... Minneapolis
Schultz, J. Harold ..... Minneapolis
Schultz, Paul E. ..... St. Paul
Schultz, Peter J. ..... Minneapolis
Schultz, Robert J. ..... Minneapolis
Schulz, Jerome E. ..... Stillwater
Schulz, Robert W. ..... Fairmont
Schulze, William M. ..... Minneapolis
Schumacher, John W. ..... Minneapolis
Schumacher, Robert V. ..... Minneapolis
† Schut, John W. ..... Anoka
Schut, Lawrence J. ..... Minneapolis

Schutt, Allan J. ..... Rochester
Schutt, Ann H. ..... Rochester
† Schwab, Peter M. ..... Rochester
Schwartz, Carl A. ..... Hastings
Schwartz, E. Robert ..... Minneapolis
Schwartzkopff, Othild ..... St. Paul
Schweiger, Theodore R. ..... Hibbing
Scott, Eugene E. ..... St. Paul
Scott, Horace G. ..... Minneapolis
Scott, Robert H. ..... Minneapolis
Scott, William R. ..... Minneapolis
† Scotti, Angelo T. ..... Rochester
Scudamore, Harold H. ..... Rochester
† Seaberg, John A. ..... Pequot Lakes
Seay, James E., III ..... Minneapolis
Sebald, John R. ..... Mankato
Seecamp, Carsten H. ..... Cambridge
Seery, Thomas ..... Rochester
† Segal, Anthony ..... Rochester
Segal, Edward L. ..... Minneapolis
Segal, Martin A. ..... Minneapolis
Segal, Marvin S. ..... Minneapolis
Segal, Sheldon J. ..... Minneapolis
† Segura, Joseph W. ..... Rochester
† Seham, Max ..... St. Paul
Seifert, Donald R. ..... Little Falls
Seifert, Gregory L. ..... Excelsior
† Seifert, Milton H. ..... Excelsior
Seifert, Milton H., Jr. ..... Excelsior
Seisler, Edward P. ..... Worthington
Sekhon, Mohan S. ..... St. Paul
† Seldon, T. Harry ..... Rochester
Seljeskog, Edward L. ..... Minneapolis
Sells, Richard J. ..... St. Paul
Selmo, Joseph D. ..... Norwood
Semba, Thomas ..... Minneapolis
Semsch, Robert D. ..... Wayzata
Sessler, Alan D. ..... Rochester
Sethre, Arthur E. ..... Fergus Falls
† Setzer, Hobert J. ..... St. Paul
Setzer, Hobert J., Jr. ..... Mankato
Severseike, Odean M. ..... Minneapolis
† Seybold, Marjorie E. ..... Rochester
Seymour, John L. ..... Minneapolis
Shackelford, Terry C. ..... Minneapolis
Shandorf, James F. ..... Minneapolis
† Shannon, William R. ..... Faribault
† Shaperman, Eva P. ..... La Mesa, CA
Shapiro, Fred L. ..... Minneapolis
Shapiro, Irving ..... Minneapolis
Shapiro, Sidney K. ..... Minneapolis
Shapiro, Stanley W. ..... Minneapolis
Shattuck, Clark A. ..... Minneapolis
Shaver, Ward ..... Fergus Falls
Shaw, Howard A. ..... Minneapolis
Shea, Andrew W. ..... Minneapolis
† Shea, John A. ..... Rochester
Shear, Howard H. ..... St. Paul
† Shearin, Robert P. N. ..... Rochester
† Sheehan, William C. ..... Rochester
Shelander, Marcus I. ..... St. Paul
Shemesh, Alvin ..... Minneapolis
† Shen, Fu-hsung ..... Rochester
Shepard, Richard ..... Albert Lea
Sheppard, Charles G. ..... St. Peter
Sheps, Sheldon G. ..... Rochester
Sher, David A. ..... Virginia
Sher, Lewis ..... Minneapolis
Sherman, Alfred G. ..... Albert Lea
† Sherman, Carnot H. ..... Bayport
Sherman, Lloyd F. ..... Minneapolis
Sherman, Royal V. ..... Red Wing
Shertzer, John H. ..... Fort Bragg, NC
Shick, Richard M. ..... Rochester
† Shih, Cheh S. ..... Rochester
† Shillington, Maurice A. ..... Ft. Lauderdale, FL
Shin, Rok ..... Howard Lake
Shirley, Raymond M. ..... Duluth
Sholler, Lawrence J. ..... Minneapolis
Shragg, Robert I. ..... Minneapolis
Shronts, John F. ..... Minneapolis
Sidell, Franklin D. ..... Minneapolis
Siebert, Darrell W. ..... Luverne
Siegel, Clarence ..... St. Paul
Siegel, John S. ..... Virginia
Siegel, Leighton G. ..... St. Paul
Siegmann, William C. ..... Minneapolis
Siekert, Robert G. ..... Rochester
Sigel, Melvin E. ..... Minneapolis
Silas, Ralph M. ..... Minneapolis
Silver, John D. ..... Minneapolis
Silverstein, Murray N. ..... Rochester
Silverstein, Paul M. ..... Minneapolis
Simison, Carl ..... Barnesville
Simmonds, Harry N. L. ..... St. Paul
† Simmons, Paul B. ..... Rochester
Simmons, Richard K. ..... Minneapolis
Simmons, Richard L. ..... Minneapolis
Simo, Kathleen Kay ..... Minneapolis
Simons, John N. ..... Rochester
Simons, Leander T. ..... St. Paul
Simonson, Donald B. ..... Minneapolis
*† Sinamark, Andrew ..... Hibbing
Singer, Benjamin J. ..... St. Paul
Singher, Lawrence J. ..... Minneapolis
Sinykin, Melvin B. ..... Minneapolis
Sipe, James W. ..... Coon Rapids
Sippe, Joseph L. ..... Rochester
† Siqueira, Aristarco ..... Rochester
† Sisco, Wm. T. ..... Rochester
Sisemore, Daniel C. ..... Rochester
Sisk, Harvey E. ..... St. Cloud
† Sisler, Clifford E. ..... Grand Rapids
† Sizemore, Glen W. ..... Rochester
Sjoding, J. Donald ..... Mankato
Sjostrom, Lawrence E. ..... St. Peter
† Skaggs, Harold, Jr. ..... Rochester
Skaife, William F. ..... Benson
Skaug, Harold M. ..... Chatfield
Skinner, Abbott ..... St. Paul
† Skinner, Harvey O. ..... St. Paul
Skinner, Ira C., III ..... San Antonio, TX
Skjold, Arthur C. ..... Minneapolis
Skogerboe, Rudolph B. ..... East Grand Forks
Slack, William J. ..... Duluth
Slanga, Roger A. ..... St. Cloud
Sletten, Richard G. ..... Minneapolis
Slocumb, Charles H. ..... Rochester
Slosser, Gaius J. ..... Minneapolis
† Smigiel, Mitchell R., Jr. ..... Rochester
Smiley, Donald P. ..... St. Paul
Smiley, John T. ..... Minneapolis
Smisek, Elmer A. ..... St. Paul
† Smisek, Frank M. ..... Minneapolis
† Smith, Adam M. ..... Minneapolis
Smith, Archie M. ..... Minneapolis
Smith, Barlow ..... Minneapolis
Smith, Baxter A., Jr. ..... Minneapolis
Smith, Cyril M. ..... Duluth

† Smith, David G. ..... Minneapolis
Smith, Don V. ..... Blue Earth
Smith, George Randall ..... Hutchinson
Smith, Graham G. ..... Minneapolis
Smith, H. Nippert ..... St. Paul
Smith, Harry J. ..... Lake Crystal
Smith, Henry T. ..... Minneapolis
Smith, John E. ..... Minneapolis
Smith, J. Weston ..... St. Cloud
Smith, Lloyd A. ..... Willmar
Smith, Lucian A. ..... Rochester
Smith, Nadine G. ..... Minneapolis
† Smith, Ralph A., Jr. ..... Rochester
Smith, Ralph E. ..... Rochester
Smith, Theodore S. ..... Minneapolis
Smith, Thorsten ..... Thiells, NY
Smith, Vernon D. E. ..... St. Paul
Smith, Wallace R. ..... Grand Marais
Smith, William T. ..... St. Paul
Smorstok, Matthew B. ..... Monticello
Smyth, John J. ..... Lester Prairie
† Smythe, Gwendolyn S. ..... Austin
Smythe, Lowell J. ..... Austin
Snider, Howard R. ..... Mankato
* Snyder, Clifford D. ..... Kiester
† Snyder, George W. ..... St. Paul
Snyder, Robert E. ..... Spring Valley
† Snyker, Omer E. ..... Ely
Soderberg, Richard J. ..... Minneapolis
† Soderlind, Ragnar T. ..... Minneapolis
† Soderstrom, Carl W., Jr. ..... Rochester
† Sohlberg, Olof I. ..... St. Paul
Soiseth, Robert P. ..... Minneapolis
Solhaug, Samuel B., Jr. ..... Minneapolis
† Soltani, Johanguir ..... Rochester
Solvason, Harold M. ..... Minneapolis
† Somerville, Gordon W. ..... Rochester
Sommer, R. K. ..... Elk River
Sommerdorf, Vernon L. ..... St. Paul
Sommers, Stephen D. ..... St. Cloud
Sondag, Glenn E. ..... Rochester
Sones, Donald A. ..... Rochester
Sonnesyn, Nels N. ..... Le Sueur
Sontag, David W. ..... Lake City
Sorem, Milton B. ..... St. Paul
Soriano, Dominador B. ..... Onamia
Soucheray, Philip H. ..... St. Paul
Soule, Edward H. ..... Rochester
† Souster, Benjamin B. ..... St. Paul
Sowada, Ernest J. ..... St. Paul
Spagnolo, Anthony A. ..... Shakopee
† Spang, Anthony J. ..... Duluth
Spang, James S. ..... Duluth
Spang, William M. ..... Duluth
Spano, Joseph P. ..... Minneapolis
Speckhals, Robert C. ..... Faribault
† Speirs, Harvey R. ..... Rochester
Spencer, Bernard J. ..... Minneapolis
† Spencer, David L. ..... Anoka
Spencer, Robert J. ..... Rochester
Sperl, Michael P., Jr. ..... St. Paul
Spiekerman, Ralph E. ..... Rochester
Spieler, F. B. ..... Pequot Lakes
† Spil, Samuel ..... Rochester
Spink, Wesley W. ..... Minneapolis
Spittell, John A., Jr. ..... Rochester
Sponsel, Kenath H. ..... Minneapolis
* Sporre, Knute A. ..... Fergus Falls
Sprafka, Gregory A. ..... St. Paul
Sprafka, Joseph L. ..... St. Paul
Sprague, Randall G. ..... Rochester
Spraitz, Anton F., Jr. ..... St. Paul
† Spurzem, Raymond J. ..... Anoka
Stadem, Clifford J. ..... Crookston
Stafne, John G. ..... St. Paul
Stahl, George W. ..... Austin
Stahler, Paul A. ..... Jordan
Stahn, Louis H. ..... St. Cloud
Stahr, Aubrey C. ..... Hopkins
Stam, John ..... Worthington
Standefer, James E. ..... Minneapolis
† Stanford, Charles E. ..... Elcho, WI
*† Stanley, Court R. ..... Minneapolis
Starkey, Thomas A. ..... Ft. Ord, CA
† Stauffer, Maurice H. ..... Rochester
Stecker, Raymond H. ..... APO New York, NY
Steffee, William P. ..... Rochester
Steidl, Richard M. ..... Minneapolis
† Stein, Paul S. ..... Rochester
† Stein, Raymond J. ..... Pierz
Stein, Robert L. ..... Northridge, CA
Stein, William A. ..... Duluth
Steinberg, Charles L. ..... St. Paul
Steiner, Andrew M. ..... St. Michael
Steiner, Leon E. ..... Albert Lea
† Steinfeld, Carroll M. ..... Rochester
Steinhilber, Richard M. ..... Rochester
† Stelter, Lloyd A. ..... Minneapolis
Stemsrud, Harold L. ..... Alexandria
Stengl, Thomas A. ..... Bemidji
† Stenseth, Jon H. ..... Rochester
† Stenstrom, Annette T. ..... Grand Marais
Stenzel, Donald A. ..... Minneapolis
Stenzel, Joseph A. ..... Minneapolis
Stephens, William E. ..... Minneapolis
Stern, Barry L. ..... San Antonio, TX
Sterner, Donald C. ..... St. Paul
Sterner, Ernest R. ..... St. Paul
Sterner, John J. ..... St. Paul
Sterrie, Norman A. ..... Minneapolis
† Stevens, John C. ..... Rochester
Stevens, Sheridan S. H. ..... Minneapolis
Stewart, Donald E. ..... Crookston
† Stewart, John W. ..... Rochester
Stewart, Marvin J. ..... Minneapolis
Stewart, Paul B. ..... Minneapolis
Stickney, J. M. ..... Rochester
Stiegler, Farrell S. ..... Minneapolis
Stifter, Anton J. ..... Winsted
Stiles, Clifford D. ..... Foley
Stillman, M. Thomas ..... Minneapolis
Stillwell, George K. ..... Rochester
† Stilwell, George G. ..... Rochester
† Stine, Harold E. ..... Rochester
Stoker, Lynn C. ..... Albert Lea
Stolee, Curtis N. ..... Fort Dauphin, Madagascar
Stolee, Thomas A. ..... St. Paul
Stolen, Keith H. ..... Grand Rapids
Stoltz, Robert C. ..... Minneapolis
Stone, Norman F. ..... Minneapolis
Stone, Stanley P. ..... Minneapolis
† Stonnington, Henry H. ..... Rochester
Storsteen, Kenneth A. ..... Duluth
Stover, Laddie E. ..... Marshall
Stoy, Robert A. ..... Little Falls
Strait, Herbert S. ..... Minneapolis
Strand, Clarence M. ..... Minneapolis
Strand, Jack W. ..... Jasper

Strand, Peter J. ..... Minneapolis
Strand, Roger W. ..... Willmar
Stransky, Theodore W. ..... Owatonna
Strathern, Carlcton S. ..... St. Peter
† Stratte, Alf K. ..... Pine City
† Stratte, Harold C. ..... Windom
Stratte, Jon R. ..... Stillwater
Strauchler, John ..... Belview
Straus, Maurice L. ..... St. Paul
Street, Bernard ..... Northfield
Streitz, John M. ..... Duluth
Strem, Edward L. ..... St. Paul
Stengl, Thomas A. ..... Bemidji
Streu, Richard E. ..... Minneapolis
Strewler, Gordon J. ..... Duluth
Strickland, Martha J. B. ..... Minneapolis
Strickler, Jacob H. ..... Minneapolis
Strobel, Claire J. A. ..... Mankato
Strobel, Jack L. ..... Minneapolis
Stroebel, Charles F., Jr. ..... Rochester
Strom, Gordon W. ..... Minneapolis
Strom, Robert L. ..... Minneapolis
Stromgren, Delph T. ..... Minneapolis
Stromme, William B. ..... Minneapolis
Strong, Cameron G. ..... Rochester
Strough, La Vern C. ..... Worthington
Strouth, Jonas C. ..... Virginia
Strunk, Clarence A. ..... Minneapolis
Struthers, Lewis E. ..... Parkers Prairie
Strutton, William H. ..... Duluth
Student, Richard E. ..... Minneapolis
Studer, Donald J. ..... Faribault
Sturges, Robert L. ..... Minneapolis
Sturley, Rodney F. ..... St. Paul
† Su, Philo S. ..... Rochester
Subak, Barbara H. ..... Minneapolis
Subby, Walter ..... Minneapolis
Sukov, Marvin ..... Minneapolis
Sulciner, Aurel ..... Minnetonka
Sullivan, W. Albert, Jr. ..... St. Paul
Summar, M. Thomas ..... Virginia
Summerskill, William H. ..... Rochester
Sun, Nora C. J. ..... Rochester
Sundberg, A. Bruce ..... Minneapolis
Sundt, Thoralf M., Jr. ..... Rochester
Sung, David T. W. ..... Rochester
† Suros, Juan ..... Rochester
Sutherland, John E. ..... Indian Head, MD
Svien, Hendrik J. ..... Rochester
† Svoboda, Wm. B. ..... Rochester
Swaiman, Kenneth F. ..... Minneapolis
Swallen, Thomas O. ..... Minneapolis
† Swanson, David A. ..... Minneapolis
Swanson, David W. ..... Rochester
Swanson, Gerald E. ..... Minneapolis
Swanson, John O. ..... Minneapolis
Swanson, Lawrence J. ..... West St. Paul
Swanson, Ralph H. ..... West St. Paul
Swedberg, William A. ..... Duluth
Swedenburg, Paul A. ..... Glenwood
† Sweetser, Horatio B. ..... Minneapolis
Sweetser, Theodore H., Jr. ..... Minneapolis
Swendseen, Carl J. ..... Minneapolis
† Swendson, James J. ..... St. Paul
Swensen, Don P. ..... Duluth
† Swenson, Arnold O. ..... Duluth
Swenson, Donald B. ..... St. Paul
Swenson, Donald B. ..... Mankato
Swenson, Floyd J. ..... Grand Rapids
Swenson, James D. ..... Edina
* Swenson, Orvie J. ..... Waseca
Swenson, Orville P. ..... Cloquet
Swenson, Richard W. ..... Minneapolis
Swenson, Roy G. ..... North Branch
Swift, Dean C. ..... Minneapolis
† Switz, Donald M. ..... Rochester
Symchych, Boris E. ..... Minneapolis
Syverson, Leslie A. ..... Fergus Falls

T

Taddeini, Luigi ..... St. Paul
Taintor, Ronald W. ..... Marshall
† Tajik, Abdul J. ..... Rochester
† Takahashi, Raymond ..... Rochester
Talsness, Jon M. ..... International Falls
Tam, Ernest C. ..... Minneapolis
Tambornino, Joseph M. ..... Minneapolis
Tanaka, Shin ..... Minneapolis
Tanasichuk, Murray A. ..... St. Paul
† Tangedahl, Tim N. ..... Rochester
Tangen, George V. ..... Minneapolis
Tani, George T. ..... St. Paul
† Tanquist, Edwin J. ..... Alexandria
Tanquist, Edwin J., Jr. ..... Alexandria
† Tapia, Hugo R. ..... Rochester
Taswell, Howard F. ..... Rochester
Tate, Wayne E. ..... South St. Paul
Taufic, Mansur ..... Austin
Tauxe, Welby N. ..... Rochester
† Taylor, Joseph H. ..... Ft. Lauderdale, FL
Taylor, Ross M. ..... Thief River Falls
Tchou, Mien-Fa ..... Minneapolis
† Teem, Martin V., Jr. ..... Rochester
Teeter, Richard R. ..... St. Paul
Teich, Kenneth W. ..... Ann Arbor, MI
Teisberg, John E. ..... St. Paul
Telander, Robert L. ..... Minneapolis
Tempel, J. W. ..... Blue Earth
ten Bensel, Robert W. ..... Minneapolis
Tenner, Robert J. ..... Minneapolis
Terrell, Bernard J. ..... Nopeming
Terrian, James C. ..... Walker
Tesch, Gordon H. ..... Elk River
Teska, Byron A. ..... Minneapolis
Tetlie, James P. ..... Duluth
† Teunis, Bernard S. ..... Rochester
Textor, Jerome ..... Minnetonka Village
Teynor, Joseph W. ..... Minneapolis
Tharp, Ralph ..... Minneapolis
Thayer, Ellsworth A. ..... Fairmont
Thalhuber, Wayne H. ..... St. Paul
Thelemann, Arthur R., Jr. ..... Minneapolis
Theobalt, Inge M. ..... Minneapolis
Theologides, Anthanasios ..... Minneapolis
† Thielen, R. D. ..... New Brighton
Thiem, Chester E. ..... Mankato
Thienes, R. Lawrence ..... St. Cloud
Thomas, John V. ..... Duluth
Thomas, Juergen E. ..... Rochester
† Thomas, William F., III ..... Rochester
Thomas, William H. ..... Minnetonka
Thomasson, Robert D. ..... Minneapolis

Thomes, A. Boyd ..... Minneapolis
Thompson, Arthur ..... Minneapolis
Thompson, A. Henry ..... St. Peter
Thompson, Carl O. ..... Hendricks
† Thompson, Gershom J. ..... Rochester
Thompson, James I. ..... Duluth
Thompson, James R. ..... Bemidji
Thompson, Robert R. ..... Willmar
Thompson, Russell A. ..... Willmar
Thompson, Thoburn F. ..... Albert Lea
Thompson, V. James ..... Staples
Thompson, Wayne W. ..... St. Paul
† Thompson, James M. ..... St. Paul
Thorsgard, Ernest O. ..... Thief River Falls
Thorson, Stuart V. ..... Minneapolis
Thurber, Deloran L. ..... Rochester
Thuringer, Carl B. ..... St. Cloud
Thurn, Roy J. ..... Duluth
Thysell, Desmond M. ..... Minneapolis
Thysell, Vernon D. ..... Moorhead
† Tiede, James J. ..... Rochester
Tietz, Charles A. ..... Virginia
Tiffany, Francis B. ..... St. Paul
Tifft, Cyril R. ..... St. Paul
† Tillisch, Jan H. ..... Rochester
Timm, Marvin E. ..... Wabasha
Tindel, Jerry R. ..... Rochester
Tinkham, Robert G. ..... Rochester
Titrud, Leonard A. ..... Minneapolis
Tobin, John A. ..... Minneapolis
Tobin, John D. ..... Minneapolis
Todd, David W. ..... APO, NY
Todd, John C. ..... Austin
Tompkins, Richard B. ..... Rochester
Tongen, Lyle A. ..... St. Paul
Torp, William B. ..... Minneapolis
Torres, Fernando ..... Minneapolis
Tosseland, Noel E. ..... Duluth
† Town, Louise A. ..... Minneapolis
Townes, C. Dwight, Jr. ..... Minneapolis
† Townsend, Gary L. ..... Rochester
Trach, Benedict B. ..... Minneapolis
† Traeger, Carl A. ..... Faribault
Trautmann, James C. ..... Rochester
Travis, James S. ..... St. Paul
Travis, Richard C. ..... Elk River
Treanor, Thomas A. ..... Albert Lea
Treat, William A. ..... Minneapolis
Tregilgas, Richard B. ..... St. Paul
† Tressler, Hubert A. ..... Rochester
† Troost, H. Bradley ..... Mankato
Trost, Francis J. ..... Minneapolis
Trotman, Neil M. ..... St. Paul
Troup, Elliott V. ..... St. Paul
Trow, James E. ..... Minneapolis
Trow, William H. ..... St. Paul
Trudeau, David ..... Austin
Truesdale, Clark W. ..... Glencoe
Tsai, Shih Hao ..... Minneapolis
Tsairis, Peter ..... Bethesda, MD
† Tschetter, Loren K. ..... Rochester
Tucker, Richard C. ..... Minneapolis
Tudor, Richard B. ..... Minneapolis
Tuma, Benjamin M. ..... Faribault
Turbak, Charles E. ..... Minneapolis
Turkbas, Nejat ..... St. Paul
† Turner, Richard H. ..... Rochester
Tveten, Omar A. ..... St. Paul
Tweedy, John A. ..... Winona
Tweedy, Robert ..... Winona
Twidwell, Joseph E. ..... Minneapolis
Twiggs, Leo F. ..... Austin
Tyce, Francis A. ..... Rochester
Tygart, Robert L. ..... Duluth

U

Ubel, Frank A. ..... St. Paul
Uhley, Charles G. ..... Crookston
† Uihlein, Alfred ..... Rochester
Ulrich, Emery E. ..... Duluth
Ulrich, Wesley D. ..... St. Paul
Ulvestad, Harold S. ..... Minneapolis
Undem, Dale ..... Alexandria
Underdahl, L. O. ..... Rochester
Utendorfer, Robert W. ..... Minneapolis
Utz, David C. ..... Rochester
Utz, Philip H. ..... LaCrosse, WI

V

Vaaler, Robert T. ..... Minneapolis
Vaccarella, R. James ..... St. Paul
Vail, David J. ..... St. Paul
Valgemae, Romil ..... Minneapolis
† Valentini, Eugene J. ..... St. Paul
† Vanasek, Richard J. ..... Rochester
Van Bergen, Frederick H. ..... Minneapolis
† van Boxel, John A. ..... Rochester
Van Cleve, Horatio P., Jr. ..... Austin
Van DeRiet, Lowell W. ..... St. Paul
Vanderpool, Thomas E. ..... Paynesville
Vandersluis, Charles W. ..... Minneota
Van Dervoort, Robert L., Jr. ..... Carswell AFB, TX
Van Druten, William A. ..... Duluth
† van Heerden, Johathan ..... Rochester
Van Herik, Martin ..... Rochester
† Van Meier, Henry ..... Stillwater
Van Ness, Noel T. ..... Ft. Jackson, SC
Van Nostrand, David M. ..... St. Cloud
Van Oppen, Dirk J. A. ..... Minneapolis
Van Puffelen, Paul S. ..... Duluth
Van Rooy, George T. ..... Thief River Falls
Van Ryzin, Donald J. ..... Duluth
Varco, Richard L. ..... St. Paul
† Vargas-Cortes, Fernando ..... Rochester
Vaughn, C. Gordon ..... St. Paul
Vaughn, Louis D. ..... Rochester
Veinbergs, Arnold ..... St. Paul
Veirs, Dean M. ..... Hastings
Vellek, Donald G. ..... Minneapolis
† Venables, Alexander E. ..... Maryville, WA
Vener, John M. ..... Arlington
Vennes, Jack A. ..... Minneapolis
Venters, Homer D., Jr. ..... St. Paul

Veranth, Leonard A. .....St. Cloud
Vermillion, Stanley E. ....Seymour Johnson AFB, NC
† Vezina, John C. .....Mapleton
Vieiralves, Gilson M. .....Winona
Vik, A. Elliott .....Minneapolis
Vilaseca, Louis B. .....Minneapolis
† Villanueva, Javier P. .....Rochester
Virnig, Hildegard J. .....Caledonia
Virnig, Mark P. .....Wells
Virnig, Richard P. .....Wells
† Visscher, Maurice B. .....Minneapolis
† Vitas, Ovidio E. .....Rochester
Vogel, Ann C. .....New Ulm
Vogel, Howard A. L. .....New Ulm
Von Droshek, Joseph C. .....Mankato
Von Drashek, Stanley C. .....Minneapolis
Von Weiss, David L. .....Minneapolis
Vorlicky, Loren N. .....Minneapolis
Votel, Thomas W. .....St. Paul

W

† Waas, Charles W. .....St. Paul
Wagner, Christian J. .....Minneapolis
Wagner, Norman W. .....Benson
Wagner, Robert M. .....Minneapolis
Wagoner, Richard D. .....Rochester
Wahman, Robert E. .....Duluth
Wahner, Heinz W. .....Rochester
† Wakim, Khalil G. .....Rochester
Walden, A. Don .....LeSueur
Walder, Harold J. .....Duluth
† Waldron, Carl W. .....Scottsdale, AZ
Waldron, John F. .....Minneapolis
† Walker, Arthur E. .....St. Paul
Walker, Frederic E., Jr. .....Minneapolis
Walker, Stuart B. .....Aurora
Wall, Carl R. .....Minneapolis
Wall, Jack E. .....Duluth
Wall, James O. .....St. Paul
Wallace, Martin O. .....Duluth
Wallace, Robert B. .....Rochester
Wallinga, Jack V. .....Minneapolis
† Walonick, Albert L. .....Hopkins
Walsh, Edward F. .....St. Paul
Walsh, John G. .....Minneapolis
Walter, Clarence W. .....St. Paul
Walter, Frederick H. .....International Falls
Walter, William E. .....Wanamingo
† Walters, Waltman .....Rochester
Wandke, Otto E. .....Fairmont
Wang, Josef K. .....Minneapolis
† Wangensteen, Owen H. .....Minneapolis
Ward, Louis E. .....Rochester
Ward, A. Neal .....Minneapolis
Warner, Clyde M. .....St. Paul
Warner, James J. .....Perham
Warner, Paul L. .....St. Cloud
Warren, Cecil A. .....St. Paul
Warren, John W. .....Minneapolis
† Warren, Michael M. .....Rochester
Wasmund, Clarence W. .....Red Wing
Wasson, Loren F. .....Alexandria
Waters, Alvin W. .....St. Paul
† Watkins, Charles H. .....Sun City, AZ
Watkins, John A. .....Wells
Watkins, Phillip C. .....Birmington, AL
Watson, C. Gordon .....Minneapolis
Watson, Cecil J. .....Minneapolis
Watson, P. Theodore .....St. Paul
Watson, Robert M. .....Morris
Watson, Robert N. .....Detroit Lakes
Watson, Sidney W. .....Little Falls
Watson, Virgil A. .....Detroit Lakes
Watson, William H. A. .....St. Paul
Watson, William J. .....Newport
Wattenberg, Lee W. .....Minneapolis
Watts, George W. .....Willard, NY
Watz, Clarence E. .....St. Paul
Weatherhead, D. Stuart P. .....Minneapolis
Weaver, Paul H. .....Faribault
Webb, Alex G., Jr. .....St. Paul
Webb, Edgar A. .....Minneapolis
Webber, Fred L. .....St. Paul
Webber, Richard J. .....Minneapolis
† Webel, Max L. .....Rochester
Webster, Lowell W. .....Minneapolis
Webster, Kirk H. .....San Antonio, TX
Wedes, Deno J. .....St. Paul
Weed, Lyle A. .....Rochester
Weeks, Richard E. .....Rochester
† Wegener, Lee T. .....Rochester
Wegleitner, Mark J. .....Denver, CO
Weick, James K. .....Camp Lejeune, NC
† Weier, Thomas E. .....St. Paul
Weigent, Charles E. .....Fort Snelling
† Weir, James F. .....Rochester
Weir, Matthew J. .....Virginia
Weis, Benjamin A. .....St. Paul
Weisberg, Martin G. .....Minneapolis
Weisberg, Maurice .....St. Paul
Weisberg, Raphael J. .....Minneapolis
Weisel, Mary Ruth .....Edina
Weiss, Carl A. .....Hastings
† Welborn, William R., Jr. .....Rochester
Welch, John S. .....Rochester
† Wellek, Mark A. .....Rochester
Wellman, William E. .....Rochester
Wellner, Theodore O. .....Rochester
† Wells, Arthur H. .....Duluth
Wells, Walter B. .....Jackson
† Welsch, John A. .....Rochester
† Welsh, George F. .....Rochester
Wempner, Jon D. .....Waconia
Wendland, John P. .....Minneapolis
Wendt, H. Paul .....Thief River Falls
Wengler, Robert A. .....Minneapolis
Wenner, Waldemar T. .....St. Cloud
Wente, Harold A. .....Rochester
† Wentworth, Albert J. .....Mankato
Wenzel, Gilbert P. .....St. Paul
† Werges, Thomas M. .....Minneapolis
Werner, Donald L. .....Hoyt Lakes
Werner, George .....Minneapolis
Wesolowski, Stanley P. .....St. Paul
† West, Catherine C. .....Edina
† West, Thomas L. .....Rochester
Westbrook, Philip R. .....Rochester
Westby, Norval M. .....Madison
Wester, Mary Sue .....Minneapolis

† Westerman, Alvin E. ..... Montgomery
† Westerman, Fred C. ..... Montgomery
† Westermeyer, Joseph J. ..... St. Paul
Westgate, Hugh D. ..... Minnetonka
Westley, Kent F. ..... Little Falls
Westmoreland, Barbara ..... Rochester
Westover, Darrell E. ..... St. Paul
Westrup, John E. ..... Lanesboro
† Wetherby, Macnider ..... Minneapolis
Wethington, Joseph F. ..... Coon Rpaids
Wett, Richard J. ..... Minneapolis
Wetteland, Thomas F. ..... West St. Paul
Wetzel, Earl V. ..... St. Paul
Wexler, Harold M. ..... Minneapolis
Wharton, William P. ..... Rochester
Wheeler, Gilbert S. ..... Virginia
Wheeler, Robert W. ..... Minneapolis
Whisnant, Jack P. ..... Rochester
Whitacre, John C., II ..... Minneapolis
White, Asher A. ..... Minneapolis
† White, Roger D. ..... Rochester
† White, Willard D. ..... Edina
White, William L. ..... Rochester
Whitesell, Lloyd A. ..... Minneapolis
Whitesell, Lloyd A., Jr. ..... Buffalo
Whiting, F. Douglas ..... St. Paul
Whitson, Sidney A. ..... Albert Lea
Whittaker, Lorin D., Jr. ..... Bloomington, IN
Whittemore, Dexter D., Sr. ..... Bemidji
Widen, Wilford F. ..... Minneapolis
Wiegand, Stewart E. ..... Atlanta, GA
Wiencke, William M. ..... St. Paul
Wiens, Alvin L. ..... Mountain Lake
Wier, G. Thomas ..... St. Paul
Wigdahl, Luther O. ..... Minneapolis
Wiger, Oliver E. ..... Little Falls
Wigg, Norman P. ..... Minneapolis
Wikoff, Howard M. ..... Crookston
Wilcox, G. Charles ..... Albert Lea
Wilcox, William A. ..... Minneapolis
Wild, John J. ..... Minneapolis
† Wilder, Kenneth W. ..... Minneapolis
† Wilder, Robert L. ..... Minneapolis
† Wilder, Russell M., Jr. ..... Topeka, KS
Wilder, Walter L. ..... Minneapolis
† Wilken, Paul A. ..... Minneapolis
† Wilkowske, Conrad J. ..... Rochester
† Wilkowske, Rudolph J. ..... Owatonna
Williams, Bruce F. P. ..... Duluth
† Williams, Charles A. ..... Seattle, WA
Williams, George E. ..... St. Paul
Williams, Harry J., III ..... St. Paul
† Williams, Henry L. ..... West St. Paul
Williams, John A. ..... St. Paul
Williams, Marland R. ..... Cannon Falls
Williams, Mervyn M. ..... Ah-Gwah-Ching
Williams, Paul A. ..... Minneapolis
Williams, Richard A. ..... St. Paul Park
Williams, Richard E. ..... Minneapolis
† Williams, W. Byron ..... Rochester
Williamson, Harold A. ..... Fairmont
† Williamson, Kenneth R. ..... Rochester
Willie, James A. ..... Albert Lea
† Willus, Frederick A. ..... Rochester
Wilmot, Cecil A. ..... Litchfield
† Wilmot, Harold E. ..... Litchfield
† Wilmont, Thomas M. ..... Rochester
† Wilson, Charles S. ..... Rochester
Wilson, David M. ..... Rochester
Wilson, Fred B. ..... St. Paul
Wilson, John A. ..... Minneapolis
Wilson, Louis J. ..... Rushford
Wilson, Robert B. ..... Rochester
Wilson, Robert E. ..... Minneapolis
† Wilson, Rolland H. ..... Winona
Wilson, Thomas M., Jr. ..... Minneapolis
Wilson, Viktor O. ..... Minneapolis
Wiltsie, John C. ..... Rochester
Winchell, Paul ..... Minneapolis
† Winders, Robert E. ..... Rochester
Windschitl, Harold E. ..... St. Cloud
† Winegardener, G. E. ..... Rochester
Wing, Elton G. ..... Sleepy Eye
Winge, Herbert C. ..... Wheaton
Winkelmann, Richard K. ..... Rochester
Winter, Laurence E. ..... St. Paul
Winter, Robert B. ..... St. Paul
† Winther, Nora M. C. ..... Columbus, OH
Wippermann, Frederic F. ..... Minneapolis
Wisiol, Erich S. ..... Minneapolis
Wisness, Osmund A. ..... Savage
Witten, David M. ..... Aberdeen, WA
Witter, Robert L. ..... Wadena
Wittrock, Louis H. ..... St. Cloud
Woellner, Richard C. ..... Minneapolis
Wohlfiel, Dwayne L. ..... Bemidji
† Wohlrabe, Arthur A. ..... Minneapolis
Wohlrabe, A. Cabot ..... Minneapolis
Wohlrabe, Clarence F. ..... North Mankato
Wohlrabe, Donald E. ..... Springfield
† Wohlrabe, Edwin J. ..... Springfield
Wohlrabe, Robert G. ..... Minneapolis
Wolfe, John W. ..... Duluth
Wolfson, Justin J. ..... St. Paul
Wolkoff, H. J. ..... St. Paul
Wollaeger, Eric E. ..... Rochester
Wolter, Frederick H. ..... Minneapolis
Wong, Edward T. ..... Minneapolis
† Wong, Terry C. Y. ..... Rochester
Wood, Lloyd T. ..... Rochester
Woodburn, Robert L. ..... St. Paul
Woodbury, John W. ..... Minneapolis
Woodley, Donald W. ..... Minneapolis
Woodruff, Whitney ..... Virginia
† Woods, John E. ..... Newtonville, MA
Woodward, Anthony H. ..... Rochester
Woolfrey, Bertram F. ..... St. Paul
Woolner, Lewis B. ..... Rochester
† Workman, Warner G. ..... Tracy
Worrell, Philip J. ..... Minneapolis
Worthington, John W., Jr. ..... Rochester
Woyda, William C. ..... Minneapolis
Wright, Donald L. ..... Minneapolis
Wright, Francis S. ..... Minneapolis
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INDICATIONS: For relief of upper respiratory and bronchial congestion associated with: the common cold, hay fever and allergies, sinusitis, influenza, and vasomotor and allergic rhinitis.

CONTRAINDICATIONS: Sensitivity to antihistamines or sympathomimetic agents. Severe hypertension or severe cardiac disease.

PRECAUTIONS: Use with caution in patients with hyperthyroidism. Patients susceptible to the soporific effects of chlorpheniramine should be warned against driving or operating machinery should drowsiness occur.

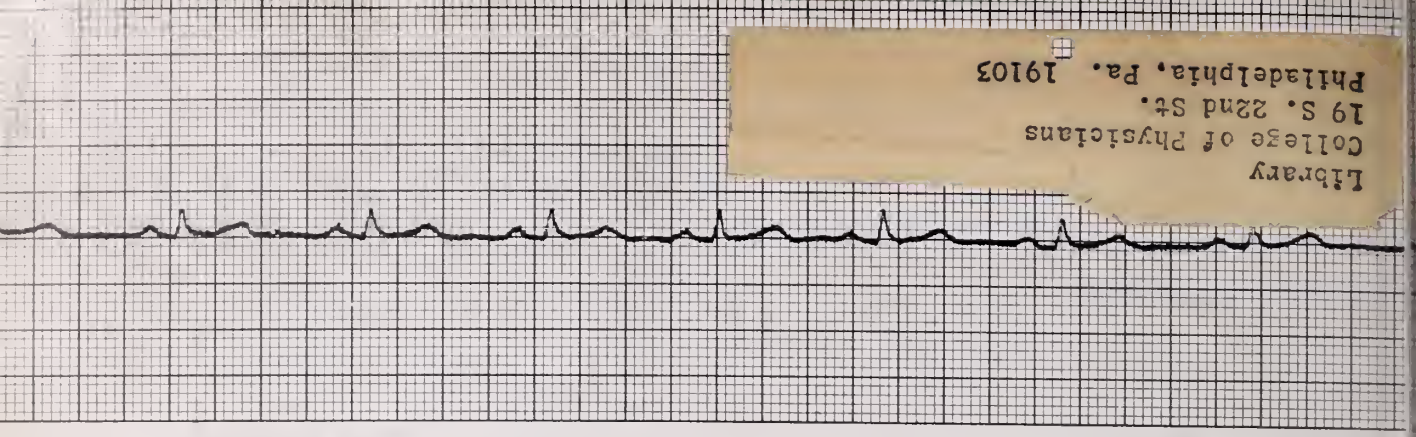
CAUTION: Federal law prohibits dispensing without prescription.

SUPPLIED: Tablets: Bottles of 100; Liquid: Pints and gallons: Timesules: Bottles of 50, 250, and 1000.

DOSAGE AND ADMINISTRATION:	Tablets	Liquid	Timesule
Adults:	1 q. 3-4 h.	2 tsp. q. 3-4 h.	1 q. 12 h.
Children 6-12 years:		1 tsp. q. 3-4 h.	
40-50 pounds:		¾-1 tsp. q. 3-4 h.	
30-40 pounds:		½-¾ tsp. q. 3-4 h.	
20-30 pounds:		¼-½ tsp. q. 3-4 h.	
15-20 pounds:		⅛-¼ tsp. q. 3-4 h.	

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When disease is ruled out and psychic tension is implicated

Valium® (diazepam) 2-mg, 5-mg, 10-mg tablets helps relax the patient and relieve his somatic symptoms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose™ packages of 1000.

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